Message

**From**: Bussard, David [Bussard.David@epa.gov]
**Sent**: 3/6/2019 8:17:18 PM
**To**: Cardarelli, John [Cardarelli.John@epa.gov]; Dunlap, David [dunlap.david@epa.gov]
**Subject**: RE: Thank You and Dose-Response Article of the Year

Thanks John. I enjoyed our conversations and interactions.
Congratulations on the award regarding your paper.
I assume our paths will cross again.

David A. Bussard

Director, Washington Division, National Center for Environmental Assessment (NCEA)
Office of Research and Development (ORD), USEPA
Tel: 202-564-4113; office RRB Room 71254

---

**From:** Cardarelli, John
**Sent:** Wednesday, March 06, 2019 2:38 PM
**To:** Bussard, David <Bussard.David@epa.gov>; Dunlap, David <dunlap.david@epa.gov>
**Subject:** Thank You and Dose-Response Article of the Year

Gentlemen,
I thought I would share this news with you. My detail ends tomorrow and I want to thank you for the opportunity to support your efforts within ORD. It was an honor working for the agency at the level I did during this detail.
Sincerely,

John Cardarelli II, PhD, CHP, CIH, PE, RSO
CAPT Public Health Service
Health Physicist
Environmental Protection Agency
ORD National Center for Environmental Assessment
26 Martin Luther King Dr., Room G-12
Cincinnati, OH 45226

Ex. 6 w c

Radiation Source Program

---------- Forwarded message ---------
From: **Kristina Moulton** <Kristina.Moulton@sagepub.com>
Date: Wed, Mar 6, 2019 at 12:52 PM
Subject: Dose-Response Article of the Year

Dear Dr. Cardarelli,

On behalf of the Editor-in-Chief, Dr. Edward Calabrese, I would like to inform you that your article "It Is Time to Move Beyond the Linear No-Threshold Theory for Low-Dose Radiation Protection" has been chosen as the #1 article of 2018 in the journal *Dose-Response*! Please accept our congratulations, and feel free to share the attached certificate.

We would also like to notify you that the Editor has granted you a waiver to use on your next submission. When you decide to use it, please include a note in your cover letter referencing this email.

Once again, congratulations on a very well-researched and well-written article. Thank you for publishing with *Dose-Response* and with SAGE!

Kind Regards,

Kristina

Kristina Moulton
*Assistant Editor, Open Access*
SAGE Publishing
2455 Teller Road
Thousand Oaks, CA 91320
USA

www.sagepublishing.com

Los Angeles | London | New Delhi

Singapore | Washington DC | Melbourne

Message

**From**: Cardarelli, John [Cardarelli.John@epa.gov]
**Sent**: 3/6/2019 7:37:51 PM
**To**: Bussard, David [Bussard.David@epa.gov]; Dunlap, David [dunlap.david@epa.gov]
**Subject**: Thank You and Dose-Response Article of the Year
**Attachments**: DOS article of the year.pdf

Gentlemen,
I thought I would share this news with you. My detail ends tomorrow and I want to thank you for the opportunity to support your efforts within ORD. It was an honor working for the agency at the level I did during this detail.
Sincerely,

John Cardarelli II, PhD, CHP, CIH, PE, RSO
CAPT Public Health Service
Health Physicist
Environmental Protection Agency
ORD National Center for Environmental Assessment
26 Martin Luther King Dr., Room G-12
Cincinnati, OH 45226

Ex. 6 W
C

Radiation Source Program

---------- Forwarded message ---------
From: **Kristina Moulton** <Kristina.Moulton@sagepub.com>
Date: Wed, Mar 6, 2019 at 12:52 PM
Subject: Dose-Response Article of the Year

Dear Dr. Cardarelli,

On behalf of the Editor-in-Chief, Dr. Edward Calabrese, I would like to inform you that your article "It Is Time to Move Beyond the Linear No-Threshold Theory for Low-Dose Radiation Protection" has been chosen as the #1 article of 2018 in the journal *Dose-Response*! Please accept our congratulations, and feel free to share the attached certificate.

We would also like to notify you that the Editor has granted you a waiver to use on your next submission. When you decide to use it, please include a note in your cover letter referencing this email.

Once again, congratulations on a very well-researched and well-written article. Thank you for publishing with *Dose-Response* and with SAGE!

Kind Regards,

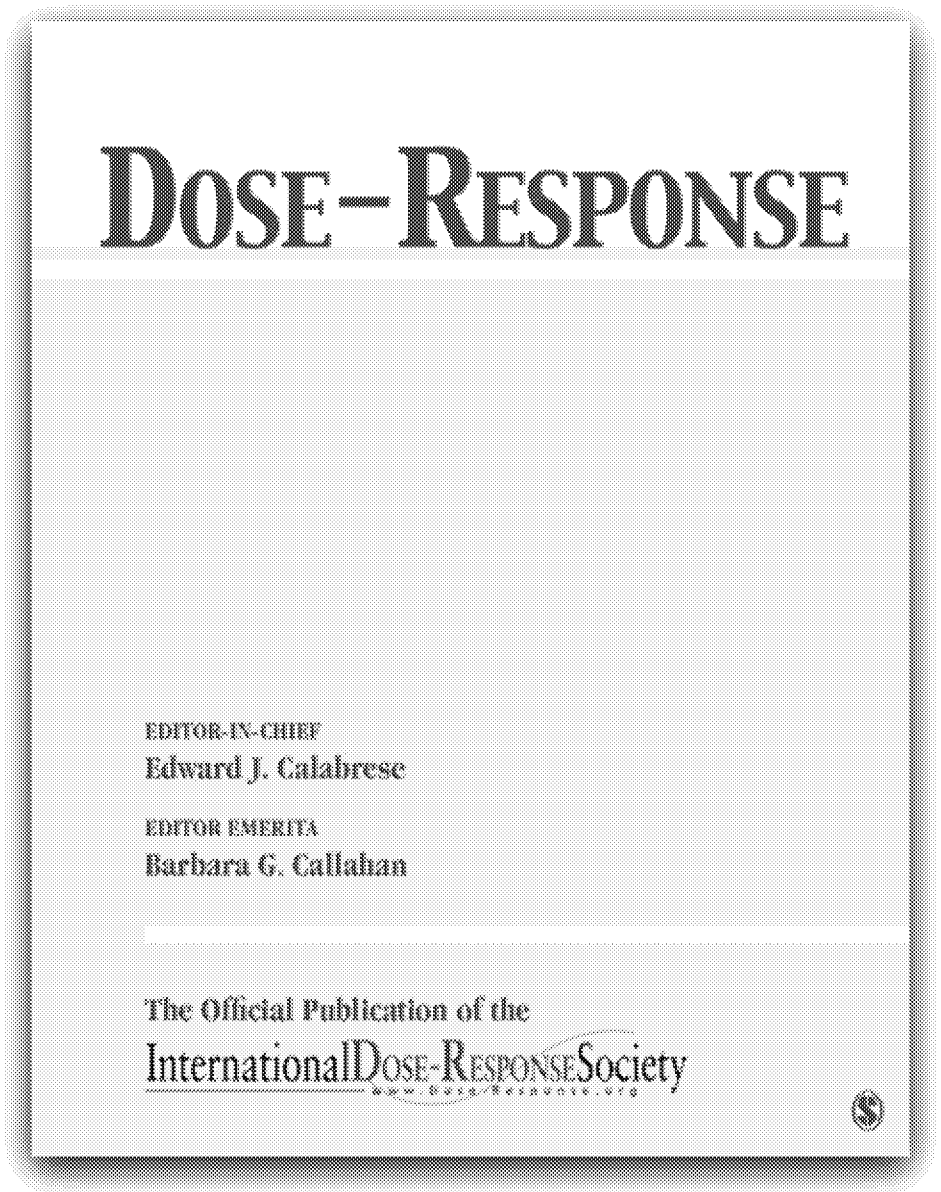
Kristina

Kristina Moulton
*Assistant Editor, Open Access*
SAGE Publishing
2455 Teller Road
Thousand Oaks, CA 91320
USA

www.sagepublishing.com

Los Angeles | London | New Delhi

Singapore | Washington DC | Melbourne



# Best Paper 2018

**Title:**

It Is Time to Move Beyond the Linear No-Threshold Theory for Low-Dose Radiation Protection

**Winners:**

John J. Cardarelli II and Brant A. Ulsh

International Dose-Response Society

**Dr. Edward J. Calabrese**
Editor-in-Chief,
Dose-Response

SAGE Publishing

Message

**From**: Cardarelli, John [Cardarelli.John@epa.gov]
**Sent**: 11/21/2018 11:59:51 PM
**To**: Dunlap, David [dunlap.david@epa.gov]
**Subject**: Re: Background Material of Our Science Committee's Project Regarding the LNT (Linear, No-threshold) Model

Yes. I see a lot of value having a call. Let me know if can do anything to support.

Sent from my iPhone

On Nov 21, 2018, at 2:59 PM, Dunlap, David <dunlap.david@epa.gov> wrote:

**Ex. 5 Deliberative Process (DP)**

DDD

---

**From:** Dunlap, David
**Sent:** Wednesday, November 21, 2018 1:39 PM
**To:** Cardarelli, John <Cardarelli.John@epa.gov>
**Subject:** Fwd: Background Material of Our Science Committee's Project Regarding the LNT (Linear, No-threshold) Model

FYI

David D. Dunlap
Deputy Assistant Administrator
EPA Office of Research & Development
Office Ex. 6 Personal Privacy (PP)

Begin forwarded message:

**From:** "McClintic, Howard" <McClintH@ctc.com>
**Date:** November 21, 2018 at 12:10:25 PM EST
**To:** "Wright, Peter" <wright.peter@epa.gov>
**Cc:** "Dunlap, David" <dunlap.david@epa.gov>, "Bob Golden Ex. 6 Personal Privacy (PP) Ex. 6 Personal Privacy (PP)
**Subject: RE: Background Material of Our Science Committee's Project Regarding the LNT (Linear, No-threshold) Model**
**Reply-To:** "McClintic, Howard" <McClintH@ctc.com>

YES, it's true – David and I know each other and he's very aware of the LNT Project for a number of years.

David remembers Dr. Robert (Bob) Golden as the leader of this Project; Bob provided me the attached item just this week. It makes plain that the Project's status and probable publication in February. The former Assistant Secretary of Nuclear Energy at DOE was Dr. Peter Lyons

(https://www.energy.gov/contributors/peter-b-lyons), who I knew when we both worked in the US Senate (he for Senator Domenici and I for Senator Baker). At DOE, Pete has your job Peter and said that "any modification of the levels of remediation due to more reasonable risk assessment per the LNT would save the US taxpayers (and the DOE, EPA and DOD) hundreds of millions of dollars annually. A 10 millirem modification would make a world of difference." Bob and I stay in touch with him and will never forget that quote.

Another individual with whom we stay in touch is Mike Honeycutt of Texas DEP. Bob reported to me yesterday that he is very excited about our progress. Our Science Committee's Report's publication is very timely, but its reception is likely to be "mixed" since there will be post-election changes in the House. These changes affect our goal of having a new Committee of the National Academy of Sciences (NAS) review (and reject) the LNT since there is ample, sophisticated science with which to formulate rules and regulations of air and water standards, far more reasonable than those derived by the LNT.

Bob and I would like to have a Conference Call with David for sure and you too, if you want to opt-in. Please review your calendar(s), off some dates and times for us to consider in order to schedule the Call.

Have a safe and warm Thanksgiving,

***Howard***

Ex. 6 Personal Privacy (PP)

**From:** Wright, Peter [mailto:wright.peter@epa.gov]
**Sent:** Wednesday, November 21, 2018 11:24 AM
**To:** McClintic, Howard
**Cc:** Dunlap, David
**Subject:** RE: Background Material of Our Science Committee's Project Regarding the LNT (Linear, No-threshold) Model

Howard

Thank you for your emails and voice mail message. I would like to introduce you to David Dunlap. David has recently join EPA as the Deputy Assistant Administrator of the Office of Research and Development. I told David that I would introduce you to him although it may be the case that you two have met before. EPA's Office of Research and Development is the office that makes the most sense to address your science related topics.

Best wishes for Thanksgiving.

Peter

Peter C Wright
Special Counsel, Office of the Administrator
United States Environmental Protection Agency
1301 Constitutional Ave NW
Washington, DC
202-566-9988

**From:** McClintic, Howard <McClintH@ctc.com>
**Sent:** Friday, November 9, 2018 10:41 AM
**To:** Wright, Peter <wright.peter@epa.gov>
**Subject:** Background Material of Our Science Committee's Project Regarding the LNT (Linear, No-threshold) Model


***Ensuring the Future Through Innovation, Science and Technology***

2711 Jefferson Davis Hwy,, Suite 620
Arlington, VA 22202

**Ex. 6 Personal Privacy (PP)**

E-Mail: McClintH@ctc.com
http://www.ctcfoundation.org


Good Day Assistant Administrator Wright:

Per my voicemail, I am writing to inform you about the singular importance of our Science Committee Report that is focused on the scientific and economic distortions caused by the LNT and the absolute need for science-based regulations (aka **transparency**). Some of our Supporters, which includes the Lignite Energy Council (ND), Bruce Energy in Canada, the NMA and several non-profits, that seek to minimize purposeless regulations.

I am certain that you have applauded changes to the membership of EPA's Science Advisory Board* as well as the April 24th, 2018 transparency initiative, propounding science-based regulations. What is common to each and both initiatives is the IS the linear no-threshold (LNT) risk assessment methodology**. The attachment demonstrates that the stark difference between regulatory standards derived by the LNT and those that are science-based. The LNT is a mathematical construct that sets regulatory limits almost at zero, which directly causes the costs of compliance

to be ridiculously, unnecessarily high (see pages 7 to 10* of the attachment, please). Further, EPA has historically, falsely claimed that its land, water and air regulations **ARE** science-based, which is patently, intellectually dishonest. The correct conclusion is that science-based regulations are more reasonable (less stringent), replicable (the definition of science), and compliance costs are millions of dollars less annually. The LNT has distorted and wrested from the US economy tens of billions of unnecessary compliance dollars over its half century history. There is only ONE way to be ABSOLUTELY confident that EPA's future health protective regulations will be wholly irrevocable and it is **NOT** by Executive Order, which is non-binding.

Rather, a new, authoritative Committee of the National Academy Sciences (NAS) needs to be empaneled to honestly evaluate the toxological and epidemiological sciences and related data to unequivocally and forcefully recommend that all EPA regulations be science-based. Our Science Committee Report inevitably will be part of the customary literature review process and readily does support this premise. Every NAS Committee's Recommendations are binding and upheld by the courts, which means the LNT will be obsolete. Thankfully, my business partner and Science Committee Co-Chair (Dr. Robert Golden), the other Co-Chair (Dr. Edward Calabrese) and I have worked at the NAS. We know the high significance of and pivotal role that our Science Committee Report will play, after being peer reviewed and, thereafter, published; its importance is international because the scientific journal in which our Report will appear is prestigious, world class, and has a global readership.

Please let's schedule a time this week for a Call.

I am grateful for your time and attention.

Most sincerely yours,

***Howard***

Howard G. McClintic
Executive Director
Ex. 6 Personal Privacy (PP)

* Michael Honeycutt, Ph.D.
Edited these pages and appointed to Head the Science Advisory Board
https://www.tceq.texas.gov/news/releases/dr-michael-honeycutt-named-chair-of-epa-science-advisory-board-1

** April 24, 2018 https://www.federalregister.gov/documents/2018/04/30/2018-09078/strengthening-transparency-in-regulatory-science

This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

www.ctc.com 1-800-282-4392

This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

Message

**From**: McClintic, Howard [McClintH@ctc.com]
**Sent**: 11/21/2018 5:10:25 PM
**To**: Wright, Peter [wright.peter@epa.gov]
**CC**: Dunlap, David [dunlap.david@epa.gov]; rgolden124@aol.com
**Subject**: RE: Background Material of Our Science Committee's Project Regarding the LNT (Linear, No-threshold) Model
**Attachments**: ATT00001.txt; FINAL LNT Introduction and Annotated TOC 11-16-18.docx

YES, it's true – David and I know each other and he's very aware of the LNT Project for a number of years.

David remembers Dr. Robert (Bob) Golden as the leader of this Project; Bob provided me the attached item just this week. It makes plain that the Project's status and probable publication in February. The former Assistant Secretary of Nuclear Energy at DOE was Dr. Peter Lyons (https://www.energy.gov/contributors/peter-b-lyons), who I knew when we both worked in the US Senate (he for Senator Domenici and I for Senator Baker). At DOE, Pete has your job Peter and said that "any modification of the levels of remediation due to more reasonable risk assessment per the LNT would save the US taxpayers (and the DOE, EPA and DOD) hundreds of millions of dollars annually. A 10 millirem modification would make a world of difference." Bob and I stay in touch with him and will never forget that quote.

Another individual with whom we stay in touch is Mike Honeycutt of Texas DEP. Bob reported to me yesterday that he is very excited about our progress. Our Science Committee's Report's publication is very timely, but its reception is likely to be "mixed" since there will be post-election changes in the House. These changes affect our goal of having a new Committee of the National Academy of Sciences (NAS) review (and reject) the LNT since there is ample, sophisticated science with which to formulate rules and regulations of air and water standards, far more reasonable than those derived by the LNT.

Bob and I would like to have a Conference Call with David for sure and you too, if you want to opt-in. Please review your calendar(s), off some dates and times for us to consider in order to schedule the Call.

Have a safe and warm Thanksgiving,

*Howard*

Ex. 6 Personal Privacy (PP)

---

**From:** Wright, Peter [mailto:wright.peter@epa.gov]
**Sent:** Wednesday, November 21, 2018 11:24 AM
**To:** McClintic, Howard
**Cc:** Dunlap, David
**Subject:** RE: Background Material of Our Science Committee's Project Regarding the LNT (Linear, No-threshold) Model

Howard

Thank you for your emails and voice mail message. I would like to introduce you to David Dunlap. David has recently join EPA as the Deputy Assistant Administrator of the Office of Research and Development. I told David that I would introduce you to him although it may be the case that you two have met before. EPA's Office of Research and Development is the office that makes the most sense to address your science related topics.

Best wishes for Thanksgiving.

Peter

Peter C Wright
Special Counsel, Office of the Administrator
United States Environmental Protection Agency
1301 Constitutional Ave NW
Washington, DC
202-566-9988

**From:** McClintic, Howard <McClintH@ctc.com>
**Sent:** Friday, November 9, 2018 10:41 AM
**To:** Wright, Peter <wright.peter@epa.gov>
**Subject:** Background Material of Our Science Committee's Project Regarding the LNT (Linear, No-threshold) Model


***Ensuring the Future Through Innovation, Science and Technology***

2711 Jefferson Davis Hwy,, Suite 620
Arlington, VA 22202

**Ex. 6 Personal Privacy (PP)**

E-Mail: McClintH@ctc.com
http://www.ctcfoundation.org


Good Day Assistant Administrator Wright:

Per my voicemail, I am writing to inform you about the singular importance of our Science Committee Report that is focused on the scientific and economic distortions caused by the LNT and the absolute need for science-based regulations (aka **transparency**). Some of our Supporters, which includes the Lignite Energy Council (ND), Bruce Energy in Canada, the NMA and several non-profits, that seek to minimize purposeless regulations.

I am certain that you have applauded changes to the membership of EPA's Science Advisory Board* as well as the April 24th, 2018 transparency initiative, propounding science-based regulations. What is common to each and both initiatives is the IS the linear no-threshold (LNT) risk assessment methodology**. The attachment demonstrates that the stark difference between regulatory standards derived by the LNT and those that are science-based. The LNT is a mathematical construct that sets regulatory limits almost at zero, which directly causes the costs of compliance to be ridiculously, unnecessarily high (see pages 7 to 10* of the attachment, please). Further, EPA has historically, falsely claimed that its land, water and air regulations **ARE** science-based, which is patently, intellectually dishonest. The correct conclusion is that science-based regulations are more reasonable (less stringent), replicable (the definition of

science), and compliance costs are millions of dollars less annually. The LNT has distorted and wrested from the US economy tens of billions of unnecessary compliance dollars over its half century history. There is only ONE way to be ABSOLUTELY confident that EPA's future health protective regulations will be wholly irrevocable and it is **NOT** by Executive Order, which is non-binding.

Rather, a new, authoritative Committee of the National Academy Sciences (NAS) needs to be empaneled to honestly evaluate the toxological and epidemiological sciences and related data to unequivocally and forcefully recommend that all EPA regulations be science-based. Our Science Committee Report inevitably will be part of the customary literature review process and readily does support this premise. Every NAS Committee's Recommendations are binding and upheld by the courts, which means the LNT will be obsolete. Thankfully, my business partner and Science Committee Co-Chair (Dr. Robert Golden), the other Co-Chair (Dr. Edward Calabrese) and I have worked at the NAS. We know the high significance of and pivotal role that our Science Committee Report will play, after being peer reviewed and, thereafter, published; its importance is international because the scientific journal in which our Report will appear is prestigious, world class, and has a global readership.

Please let's schedule a time this week for a Call.

I am grateful for your time and attention.

Most sincerely yours,

***Howard***

Howard G. McClintic
Executive Director
Ex. 6 Personal Privacy (PP)

* Michael Honeycutt, Ph.D.
Edited these pages and appointed to Head the Science Advisory Board
https://www.tceq.texas.gov/news/releases/dr-michael-honeycutt-named-chair-of-epa-science-advisory-board-1

** April 24, 2018 https://www.federalregister.gov/documents/2018/04/30/2018-09078/strengthening-transparency-in-regulatory-science

This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

www.ctc.com 1-800-282-4392

This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

www.ctc.com 1-800-282-4392

# Comparison of the Scientific Basis of the Linear No Threshold (LNT) Model with Threshold Models for Cancer Risk Assessment of Radiation and Chemicals

## Introduction

The linear no-threshold (LNT) single hit dose response model for carcinogenicity has dominated regulatory risk assessment of radiation and carcinogenic chemicals from the mid-1970s to the present day. Essentially by definition, the fundamental biological assumptions on which the model relied at the time of its early adoption clearly reflected a primitive understanding of the biological processes controlling mutation and genetic injury and their ultimate association with cancer. However, the astonishing breakthrough advancements contributed by modern molecular biology over the last several decades now provides not only the experimental tools but also conclusive evidence substantively undermining the LNT model for science-informed cancer risk assessment. It is now known with certainty that DNA is not simply an inert chemical target such that even a single "hit" potentially results in cancer. Instead, all biological systems mount aggressive, integrative, and holistic defenses to a plethora of always present endogenous and exogenous attacks to its core genetic and biological functions. These consist of overlapping defenses that are essential for sustaining cell and organism homeostasis all of which are activated by low doses/dose rates of ionizing radiation, operate at the molecular, cellular, tissue, and whole-body levels. Noteworthy is that the 2015 Nobel Prize for chemistry was awarded to three scientists from the Francis Crick Institute, Duke University and the University of North Carolina for their detailed mechanistic studies of three different kinds of DNA repair (i.e., base excision repair, mismatch repair and nucleotide excision). As discussed in this review, these and other complimentary cellular mechanisms which describe the evolutionarily conserved and multilayered processes with the sole purpose of protecting DNA integrity. This vast body of knowledge collectively challenges the notion that LNT is a scientifically valid descriptor of any meaningful biological event. This is particularly the case for potential adverse responses for either radiation or chemicals in the low dose (exposure) range. Based on a robust, and growing, understanding of potential biological effects at all levels of biological organization, it is timely to examine the impact of this vast body of knowledge on the scientific legitimacy of continued reliance on the LNT model as a scientifically defensible driver of carcinogen risk assessment.

## Annotated Table of Contents

**Papers submitted for Special Issue of Chemico-Biological Interaction (CBI)**
**Current Status; publication date: 2/19**

Golden, R. **Dedication and Prologue** **Status: Submitted**

Golden, R., Bus, J. and Calabrese, E. **Introduction** **Status: Submitted**

Calabrese, E. **The Linear No-Threshold (LNT) Dose Response Model: A Comprehensive Assessment of its Historical and Scientific Foundations.** The LNT model for cancer risk assessment is assessed with respect to its historical foundations, particularly the belief that ionizing radiation-induced gene mutation was cumulative, irreversible and displayed a linear



ED_002751_00000007-00001

dose response. **Status: Undergoing review**

Costantini, D. and Borremans, B. **The Linear No-Threshold Model is Less Realistic than Threshold or Hormesis-Based Models: An Evolutionary Perspective** The LNT model as applied to biological effects of low and moderate stressor levels has less biological validity than either threshold or hormetic models. Both empirical and theoretical evidence from ecological and evolutionary disciplines are employed to evaluate how exposure to mild amounts of stress has been of paramount importance for the evolution of life on earth. The implications of such findings for LNT are explored in depth. **Status: Accepted**

Scott, B. **The LNT Model for Cancer Induction is Not Supported by Radiobiological Data** This paper reviews a number of well-established adaptive mechanisms at all levels of biological organization and their implications for assessing cancer risk after exposure to low radiation doses/dose rates. **Status: Undergoing review**

Brooks, A. **The Impact of Dose Rate on the Linear No Threshold Hypothesis.** This paper evaluates the role of radiation dose/dose rate at the molecular, cellular, tissue and whole organism levels and demonstrates how they impact cancer risk assessment at low doses. **Status: In revision, following peer review**

Tharmalingam, S., S. Sreetharan, Brooks, A. Boreham, D.R. **Re-evaluation of the Linear No-threshold (LNT) Model using New Paradigms and Modern Molecular Studies.** This review summarizes the potential effects of ionizing radiation in the low dose range. Addressed are a variety of cellular defense mechanisms including DNA repair, programmed cell death (apoptosis), cell cycle arrest, senescence, adaptive memory, bystander effects, epigenetics, immune stimulation, and tumor suppression and how they affect the nature of the dose response in the low dose zone for ionizing radiation. **Status: In revision, following peer review.**

Andrew M. Zarnke, A.M., Tharmalingam, S., Boreham, D.R. and Brooks, A.L. **BEIR VI Radon: The Rest of the Story.** This paper evaluates the risk of lung cancer from residential radon in homes and re-examines the EPA risk assessment logic and process for radon. **Status: In revision, following peer review.**

Kobets, T. and Williams, G. **Review of the Evidence for Thresholds for DNA-Reactive and Epigenetic Experimental Chemical Carcinogens.** This paper reviews key dose-response and mechanistic data for numerous potent DNA-reactive or epigenetic chemical carcinogens for both precursor effects and cancer-causing potential. Key experimental data, including relevant mechanistic data, for potent DNA-reactive or epigenetic chemical carcinogens are reviewed. At non-toxic dosages, there are thresholds for induction of cancer by all types of potential chemical carcinogens. **Status: In revision, following peer review.**

Clewell, R., Thompson, Chad, Clewell, H. **Mechanistic Aspects of Chemical Carcinogens Demonstrating Thresholds.** Numerous subcellular components play key roles in mitigating potential damage to DNA as a consequence of exposures to a variety of DNA-reactive chemicals. This paper discusses the p53 DNA damage response toxicity pathway which is



ED_002751_00000007-00002

involved in a variety of subcellular processes including chemical-specific differences in transcriptional activation. **Status: In revision, following peer review.**

Ricci, P. and Tharmalingam, S. **Ionizing Radiation Epidemiology does not Support the LNT Model** Using a novel graphing approach, abundant data from a variety of sources including medical imaging, airline pilots, high natural background radiation areas, radiation workers, and the extensive data on atomic bomb survivors are used to assess exposure-response aspects of potential cancer mortality. **Status: In revision, following peer review.**

Williams, R.A. **Economic Benefit-Cost Implications of the LNT Model.** Using two data-rich illustrative examples (i.e., radon and formaldehyde) this paper contrasts benefit-cost implications of LNT vs threshold models. **Status: Submitted**



ED_002751_00000007-00003

Message

**From**: Dunham, Sarah [Dunham.Sarah@epa.gov]
**Sent**: 5/16/2017 12:55:30 AM
**To**: Jackson, Ryan [jackson.ryan@epa.gov]; Dravis, Samantha [dravis.samantha@epa.gov]; Brown, Byron [brown.byron@epa.gov]; Bolen, Brittany [bolen.brittany@epa.gov]
**CC**: Gunasekara, Mandy [Gunasekara.Mandy@epa.gov]; Lewis, Josh [Lewis.Josh@epa.gov]; Page, Steve [Page.Steve@epa.gov]; Grundler, Christopher [grundler.christopher@epa.gov]; Edwards, Jonathan [Edwards.Jonathan@epa.gov]; Harvey, Reid [Harvey.Reid@epa.gov]
**Subject**: OAR submission to EPA's Regulatory Reform Task Force per EO 13777
**Attachments**: Transcript of EPA Office of Air and Radiation Stakeholder Conference Call (held 4.24.2017).pdf; ATT00001.htm; OAR Memo Executive Order 13777 FINAL_5_15_17.pdf; ATT00002.htm

Please see attached OAR's EO 13777 submission for consideration by EPA's Regulatory Reform Task Force. Also attached is the transcript of the public stakeholder meeting held on April 24.

**EPA**

**Moderator: Andrea Drinkard**
**April 24, 2017**
**11:00 a .m. ET**

Operator: This is conference # 8535873.

Good morning. My name is (LaShonda), and I will be your conference operator today.

At this time, I would like to welcome everyone to the Executive Order 13777 on Enforcing the Regulatory Agenda.

All lines have been placed on mute to prevent any background noise. After the speakers' remarks, there will be a question-and-answer session. If you would like to ask a question during this time, simply press star then the number 1 on your telephone keypad. If you would like to withdraw your question, press the pound key.

Thank you. I would now turn today's call over to Andrea Drinkard to begin. Please go ahead.

Andrea Drinkard: Thank you, (LaShonda), and thank you everyone for joining us today. I am Andrea Drinkard, deputy communications director for the Office of Air and Radiation.

Let me start by providing an overview of the structure of today's call. First, we will hear a few minutes of opening remarks from Sarah Dunham, acting assistant administrator for the Office of Air and Radiation.

Following Sarah's remarks, I will provide a summary of the logistics for today's call, and then we'll turn it over to you, our stakeholders. Let's get started.

Sarah Dunham: Thank you, Andrea. Good morning, and thank you for joining us. My name is Sarah Dunham, and I'm the acting administrator for the Office of Air and Radiation at EPA.

On February 24, 2017, President Trump issued Executive Order 13777 on Enforcing the Regulatory Agenda. The Executive Order, among other things, requires each agency to create a Regulatory Reform Task Force to evaluate existing regulations and identify any that should be repealed, replaced or modified.

To inform these recommendations, EPA is holding today's public meeting so we can hear from those directly impacted by our regulations, including federal, state, local and tribal governments, small businesses, nongovernmental organizations and trade associations.

We invite you to take this opportunity to share your views here today. We also invite you to submit your comments to EPA's Regulatory Reform Docket, EPA-HQ-OA-2017-0190. The docket, which is accessible through www.regulations.gov, will remain open through May 15, 2017.

We will give equal consideration to input provided through the docket or through this teleconference. Your input as well as that received through other meetings and written comments will inform EPA's Regulatory Reform efforts and help fulfill the EPA's commitment to complying with Executive Order 13777.

Today's teleconference is not the only meeting EPA is holding on Regulatory Reform. The administrator has also directed the other EPA offices to provide recommendations and consult with their stakeholders and doing so. A list of EPA's planned meetings can be found on our regulatory reform website, www.epa.gov/laws-regulations/regulatory-reform.

Under the Executive Order, the Regulatory Reform Task Force is asked to provide a report to the administrator detailing the agency's progress by May 26th.

Once again, thank you for joining us today. I'm going to turn it back over to Andrea for some logistics for today's call.

Andrea Drinkard: Thank you, Sarah.

And as we said, today's call is an operator-assisted teleconference. As the operator has said, if you wish to speak at any time, you may nominate yourself to speak by hitting star-1 on your phone. Your name will be added to a queue. Speakers will be asked to deliver up to three minutes of remarks. You will hear a chime when you have 30 seconds remaining. When you hear that sound, please start wrapping up.

In order to hear from as many stakeholders as possible, we will be adhering strictly the three-minute time limit. If you continue to be on three minutes, we may interrupt you so that we may -- we can move on to the next speaker.

We will be hearing until 2 p.m., and we will do our best to hear from everyone who wishes to speak. As a reminder, this is EPA's opportunity to hear from you, our stakeholders. We will be in listening mode and will not be answering questions about specific rules or actions.

If you do not have an opportunity to speak on the call or you have additional remarks to go beyond the three-minute time limit, please submit your input to the EPA docket as Sarah said. EPA will be giving equal consideration to input provided through either of these methods.

And with that, we'll turn it over to the operator who will compile the list of questions.

(LaShonda)?

Operator: At this time, if you would like to ask an audio question, please press star-1 on your telephone keypad. We'll pause for just a moment to compile the Q&A roster.

OK. And our first question comes from the line of Cindy Folkers with Beyond Nuclear.

Cindy Folkers: Hi, can you hear me? Hello?

Andrea Drinkard: Yes, we can hear you.

Cindy Folkers: Hi. Yes, I actually had a comment so we can give those now?

Andrea Drinkard: Yes.

Cindy Folkers: OK. I'm Cindy Folkers from Beyond Nuclear. Thank you for the opportunity to comment today.

Executive Order 13777 is asking to, quote, "alleviate unnecessary regulatory burden placed on the American people," unquote. For Americans, radioactivity from the 19th and 20th century energy sources we've been using remains a health burden, and current regulations are not protective enough for women, children and pregnancy.

Adult males are more resistant to radiation than adult females who are less sensitive than male children who are, in turn, less sensitive than their female counterparts. That means that -- that means that for the same dose of radiation, women and children suffer more cancers than men. But more troubling the dataset on which this health information is based does not account for constant contamination of air and water that results from nuclear and coal technologies or exposures resulting from inhalation or ingestion. These data also represent just cancer and do not include non-cancer impacts.

Pregnancy, a uniquely vulnerable life stage, is not fully represented in this data and not fully protected by our current radiation standards. If EPA wants to streamline their regulation, they should modify them to protect the most

vulnerable life stages, which are pregnancy and childhood and get rid of more complicated less protective exposure standards. EPA should assume that pregnancy is a constant state in the population and set any radiation standards to protect it.

Do EPA radiation protection standards place an undue burden on the American people? For women, children and pregnancy, the answer is yes, because the exposure standards fail to protect them adequately.

Just as important, we are at the -- we are at the precipice of energy decisions, which will change our environment and civilization as we know it. EPA needs to encourage efforts that inform the public of this increased scientifically validated health burden on women and early life stages. That way the public and politicians can factor this information into decisions for our energy future and understand that continuing use of coal energy or using nuclear power to combat climate change means asking already overburdened women and children to continue to pay a higher health price.

Thank you for the opportunity to comment, and I will be submitting formal written comments by the May 15th deadline.

Andrea Drinkard: Excellent. Thank you very much for your input.

Operator, would you please open the next line?

Operator: Our next question comes from the line of Anne Gobin with Connecticut Department of Environment.

Anne Gobin: Good morning. Anne Gobin, I'm the director of Connecticut Air Program. Like EPA, our mission is to protect the health and wellbeing of all people and the environment. Although we've made great progress, our air is not clean and we continue working hard to reduce our carbon footprint by burning less fossil fuel.

EPA needs to continue on this positive path to achieve clean air standards and address climate change. No regulation should be struck without a replacement

that achieves as much, if not more protection of public health and the environment. Connecticut's population is exposed to an unacceptable risk from air pollution. More needs to be done.

EPA should be addressing additional rules -- should be adopting additional rules to address air pollution problems and fulfill its obligations under the Clean Air Act. The Good Neighbor Provision has not been fully implemented as required. Interstate transport has not been effectively regulated.

Both EPA and state and local air programs need to be adequately funded to fulfill the obligations we have. The proposed cuts, if implemented, would devastate our efforts. We're already inadequately funded to carry out our obligations to protect public health and the environment under the Clean Air Act.

Funding increases are needed. Cuts will prevent us from fulfilling our obligations.

Thank you for the opportunity to comment.

Andrea Drinkard: Thank you, Anne.

Operator, would you open the next line please?

Operator: Certainly. Our next comment comes from the line of Scott Lewit with Structural Composites.

Scott Lewit: Hi, good morning. Thank you for taking my call. Scott Lewit, president of Structural Composites and Compsys, Inc. We're located down here in Melbourne, Florida; a small business with about 70 employees.

We've been impacted by the SNAP rule. This is concerning for us. Basically, what's happened is they take ozone regulations and now apply them to greenhouse gases.

We use urethane foam in our process that requires 134A as a blowing agent. And, you know, we've had to change blowing agents in the past under EPA rules like from R22 to the less harmful 134A. And in that transition and the prior ones, we had an alternative.

The difference this time is we do not have an alternative, and EPA has forced us to commit to a date with no alternative. With that, we had no alternative but to sue the EPA, and we currently have a lawsuit with the EPA.

As we've gone in with the National Marine Manufacturers Association, our industry trade group, numerous meetings with the EPA, basically we've run into a hard wall where the past administration has refused to look at any logic whatsoever. The EPA has an inability to distinguish between recurring and non-recurring pollution. This technology that we're generating funded by the Small Business Administration, SBI, our program for the Navy, has resulted in weight savings in transportation for semi-trailers up to 20 percent and installation qualities up to 40 percent higher.

We can show that we can offset the greenhouse gases in as little as two years to fuel savings. However, the EPA will not look at this.

So what we're asking is three things. We think the SNAP should not be applied to ozone -- you know, should not -- greenhouse gases should be segregated from ozone regulation, and SNAP should not be applied to regulation of 134A.

Subject to that notwithstanding, we would request a narrow use limitation to allow us to continue to make our product, which again we can demonstrate has profound impact on greenhouse gas, not to mention light weighting, reduced wear and tear on roads and longevity.

We also ask that the methods be evaluated so that the EPA and Department of Energy can work together and look at recurring and non-recurring pollution so that we can make smart decisions. If we make a windmill, it takes some time to make it. We're going to have some environmental impact. And with that,

we can offset that environmental impact with electricity generation. We got to make those tradeoffs. That's what's happening here in Transportation.

We're lighter, more efficient, longer lasting. We can show the benefit, but the EPA really put blinders on and will not look at these tradeoffs.

Thank you for taking my comment.

Andrea Drinkard: Thank you very much, Scott.

Operator, would you open the next line?

Operator: Our next comment comes from the line of Laura Bender with American Lung Association.

Laura Bender: Thank you. My name is Laura Kate Bender. I'm the director of Advocacy for the Healthcare Campaign with the American Lung Association. We're the nation's oldest voluntary health organization, and our mission is to save lives by improving lung health and preventing lung disease.

EPA is to be seeking input today on existing regulations that could be made less burdensome. I'm speaking today to represent the more than 125 million Americans who live in places with unhealthy air. These Americans are currently shouldering the burden of air pollution. They rely on EPA standards to monitor and adjust to air quality in their communities. On their behalf, the Lung Association asks EPA not to block, weaken or delay existing protections under the Clean Air Act.

To encourage citizen participation in this process, we also request that EPA expand opportunities for public comments.

The timing and format of today's hearing made it challenging for many stakeholders to join, so I'm going to share two of their stories.

(Laura Paul) and her son (Tyler) live in Clarendon, Texas, and rely on EPA's current Clear Air Standards. Here are some comments from (Laura).

I quote, "My son (Tyler) was healthy when he was born, but around one year of age he began getting sick all the time. He was later diagnosed with asthma and over the years, he has been hospitalized more times than I can count. Fortunately, now that (Tyler) is 14, his condition has stabilized, but we still have to be vigilant. When your child has asthma, you never stop worrying. Every time your child goes to school, into a friend's house, you're aware that poor air quality or some other unexpected situation could put him or her in danger, and you might not be there to help.

Scientists and doctors tell us it's risky for children with asthma to inhale pollutants. (Tyler)'s lungs are already sensitive. When he breathes in a powerful irritant like ozone, his lung tissue swells further, making it harder for him to breathe. He coughs and (leads into) struggles. And we know how quickly a severe asthma attack can become a life-threatening emergency.

As a mother, I'm deeply saddened and if there's even a possibility that EPA would weaken air pollution standards, rolling back limits in ozone and other danger pollution would put our children in harm's way. On behalf of mothers everywhere, I urge EPA to do its job by maintaining strong air pollution limits and continuing to enforce life-saving measures to clean it up," end quote.

Now I'd like to share a few comments from (Tyler Paul), (Laura)'s son. I quote, "If you never had asthma, you can't imagine what it feels like to not be able to breathe. Picture being under water and something is preventing you from getting to the surface.

I've had asthma since I was a very little kid. Now that I'm 14, I'm happy that my asthma is under control, but I know that it can change at any time. I can't pretend I don't have it because my asthma will never go away.

I want to testify on behalf of all kids with asthma. Air pollution makes it harder for kids like me to breathe. I may only be 14, but I know that I have a right to clean air. That's why I'm speaking up today. I hope that what I've had to say will make a difference," end quote.

On behalf of the American Lung Association and the people in communities we serve, including families like (Tyler)'s, we strongly urge EPA to defend and enforce life-saving protections under the Clean Air Act. We will also submit detailed written comments for the record.

Finally, to request that EPA offer expanded opportunities to submit comments. Thank you.

Andrea Drinkard: Thank you, Laura.

Operator, next line?

Operator: Our next comment comes from the line of David Doniger with NRDC.

David Doniger: Thank you very much. On behalf of NRDC's three million members and supporters, I want to register a strong opposition to the Trump administration's destructive and unpopular agenda of rolling back public health and environmental safeguards.

We have a shared moral obligation to provide clean air and a safe and healthy climate for future generations, but I don't rest my case there. The Clean Air Act is the finest public investment with the best rate of return for the American people. It has prevented more than 160,000 deaths and 1.7 million asthma attacks each year.

Over its 50-year history, the Clean Air Act has saved literally millions of lives and averted tens of millions of serious illnesses. The Clean Air Act has prevented environmental catastrophes ranging from the loss of lakes and forests to acid rain, massive ozone-induced crop and forest damage and destruction of the ozone layer.

Taking the lead out of gasoline has protected millions of kids from brain damage, and it's copied all around the world.

In purely economic terms, it's air pollution that is a job killer. Without the Clean Air Act, American workers would lose 13 million more work days to illness every year. Tens of millions of work days lost for adults and tens of millions of school days lost for children have been avoided over the last five decades by the Clean Air Act.

The -- more than 2.5 million people in America already work in clean energy. That's triple the number in the coal, oil and gas industries. And the Clean Air Act delivers up to $90 in public health benefits for every dollar invested in curbing pollution.

The job isn't done. We specifically object to the plans to roll back the Clear Power Plan, the Clean Car and Truck Standards, the Mercury and Air Toxic Standards, EPA's Methane Standards. Unfortunately, I could go on.

Americans did not vote to roll back clean air, clean energy and climate safeguards. The polls show that strong majorities -- including majorities of Trump voters -- want to keep or strengthen clean air and climate safeguards, energy efficiency measures, water pollution safeguards and my statement will summarize that polling.

I call on you to stop this sham. You're cramming public input on clean air into a three-hour teleconference run out of Washington.

By contrast, EPA held literally hundreds of stakeholder meetings and public hearings in multiple cities, over the course of three years to get all sides' input into just one regulation, the Clean Power Plan.

Abandon this roll back process and get back to doing your job.

The Back2Basics course that Administrator Pruitt has charted…

Andrea Drinkard: (Excuse me), David, your…

David Doniger: …is a Back2Pollution detour.

Andrea Drinkard: David, your time is up.

David Doniger: Thank you.

Andrea Drinkard: Thank you very much.

Operator, would you open the next line?

Operator: Our next comment comes from the line of Timothy Hunt with the American Wood Council.

Timothy Hunt: Yes, my name is Tim Hunt. I'm the senior director of Air Quality Programs at the American Wood Council. AWC is the voice of North Americans wood products manufacturing, representing over 75 percent of an industry that provides approximately 400,000 men and women in the United States with family wage jobs. AWC makes products that are essential to everyday life from a renewable resource that absorbs and sequesters carbon.

We believe EPA should address the rapidly developing air permitting gridlock under the Clean Air Act by adopting more flexible policies and use of more realistic commissions data and modeling tools that will protect the environment and public health.

Every five years we must -- EPA must decide whether the National Ambient Air Quality Standards are sufficiently protective of public health. Recently, EPA has systematically tightened the NAAQS for several standards. Traditionally, the focus of the program has been on states developing plans to improve air quality in non-attainment areas, usually cities to meet the NAAQS.

However, since the NAAQS are effective immediately in rural areas where we operate, mills contemplating expansions or modifications that trigger a permitting review must demonstrate that emissions from the mill when combined with background air quality do not exceed the applicable NAAQS standard in order to obtain a permit. This results in a permit stalemate.

When the NAAQS levels, having dropped closer to background levels, is becoming more difficult to, quote, "pass the test and get an approved permit." To prevent further ratcheting, EPA should not lower standards further until current standards are fully implemented and met. During this time, air quality will continue to improve under current programs.

The inability to permit a project hurts the competitiveness of the mill, harms product development, prevents meeting customer needs and hampers innovation, and it thwarts environmentally beneficial projects which can lower emissions. Local communities will miss out on new job and economic growth while industry faces the risk of becoming uncompetitive in the global marketplace of wood products. The decline of permit submittals to states is a strong indication of this growing problem. Adapting new permitting policies by EPA could help alleviate the problem.

The challenges with the (ever-tightening) NAAQS are exacerbated by a lack of or inappropriate emission measurement methods, poor estimates of emissions, use of unrealistic air dispersion models and several rigid permitting policies.

AWC has provided EPA several suggestions in the recent past and will do so again including lower and fugitive P.M. emission estimates, acknowledging limited emissions from intermittent sources and using more realistic receptor locations. EPA's own recognitions of the advantages of probabilistic tools in its ORD report from 2014 should be incorporated into the permitting guidance to replace older deterministic approaches and avoid overestimates.

Finally, EPA should reestablish its partnership with states and give them more latitude to advance new approaches…

Andrea Drinkard: Thank you, Tim. Your…

Timothy Hunt: …and models.

Andrea Drinkard: …time is up.

Timothy Hunt: Thank you.

(Off-mic)

Andrea Drinkard: If you have more comments, you can submit them to the Docket. Thank you.

Operator, would you open the next line?

Operator: Certainly. As a reminder, to make a comment, please press star-1 on your telephone keypad.

Our next comment comes from the line of Albert Donnay with Donnay (Toxicology).

Albert Donnay: Thank you. My name is Albert Donnay. I'm a consulting toxicologist testifying today on my own behalf.

A regulation that I'm asking EPA to repeal or modify the Clean Air Act's National Ambient Air Quality Standards for carbon monoxide. The next lower reliable C.O. exposure from 100 parts per million to just 9 parts per million average over eight hours and 35 ppm over one hour. EPA has cited these standards since 1975 as the basis for requiring catalytic converters on vehicles to convert C.O. to CO2.

This regulation has caused American car buyers over $80 billion in the last 40 years, but the C.O. NAAQS has never been based on any studies showing that outdoor C.O. levels ever posed any health hazards to anyone nor on any studies showing that C.O. exposures below the NAAQS limits are safe.

In our latest review published in 2011, EPA said only six human exposure studies published in the 80's and 90's, five of them commissioned or conducted by EPA where sufficient quality to be cited as the basis of the C.O. NAAQS, but none tested any eight-hour C.O. exposures and their one-hour exposures were all above the EPA's one hour 35 ppm limit.

In the largest study (inaudible) with heart disease, C.O. exposures varied from 42 to 357 parts per million, while smaller studies exposed 96, five men and five women total to C.O. from 50 to 200 ppm. But since they are reported finding adverse effects in people with heart disease at these levels, none provided any assurance that EPA's lower limits are low enough to prevent such outcomes.

Over 200 air pollution epidemiology studies that included C.O. in their analysis suggest otherwise. They almost all report finding significant health effects associated with small increases in C.O. far below the NAAQS limits and within the range of 1 to 2 ppm that now prevail in most cities. But Administrator Jackson excluded these and all other types of C.O. studies from being cited as the basis for the NAAQS in the last review.

More than 15,000 studies in all even at the six studies she cited had tested relevant C.O. levels at or below the NAAQS limits instead of above them. Other aspects of the design undermining the result and (test out) on their fitness for policymaking. None preserved their data. Five used their quality control lab that could not reliably produce its results for a critical carboxyhemoglobin measurements, and all six of them mistook the subjects being as carboxyhemoglobin as an independent measure of C.O. uptake when it's actually a measure of C.O. excretion and dependent on their actual arterial COHb, which they didn't measure.

For all these reasons, I ask EPA to revoke or at least suspend the C.O. NAAQS until a new C.O. Clean Air Scientific Advisory Committee can be appointed to consider all the peer-reviewed articles published on C.O....

(Crosstalk)

Albert Donnay: ...for last review. Thank you. And (inaudible) some new limits if needed based on studies whose data are available for independent review. Thank you.

Andrea Drinkard: Should we -- operator, (move) over the next line?

Thank you, Albert.

Operator: Our next comment comes from the line of Scott Evans with Clean Air Engineering.

Scott Evans: Hi, this is Scott Evans from Clean Air. I'd like comment on the EPA's use of guidance documents to implement rulemaking.

On EPA's Emission Measurement Center website, there are a series of EMC guideline documents that have been collected by EPA since 1988. They're currently numbered now one through 53 with a few gaps in them, and these are guidance on a variety of monitoring and emission measurement issues.

My problem is that many of these currently are technically obsolete. There appears to be no mechanism for ongoing review for relevance or obsolescence. For example, one particular guidance document that is causing me particular problem is GD33, which has to do with Test Methods 25 and 25A. I believe that it is an obsolete document.

The unfortunate part is that these guidance documents turn into the rule of law even though they are called "guidance documents" because they appear, they are relied on by states, for example, and state permits. They are relied on when doing other rulemakings in terms of SPS or MACT rules. And so these guidance document are taken at face value and not periodically reviewed apparently.

But more importantly, they seem to be contrary to the Administrative Procedures Act. I'll read one sentence on the website that contains these documents. The last sentence in the introductory paragraph says, "Some of the guidance may result in changes to the methods or performance specification." This is the part that I believe is contrary to the Administrative Procedures Act, which requires notice and comment rulemaking for all changes to methods and performance specification.

I would propose that EPA rescind all of these guideline documents unless EPA can come up with a compelling reason why they cannot submit them to

the notice and comment rulemaking procedure. And thank you very much for the opportunity to provide these comments.

Andrea Drinkard: Thank you very much, Scott.

Operator, next line please?

Operator: Our next comment comes from the line of Andrea Field with UARG.

Andrea Field: My name is Andrea Field. I'm making this statement on behalf of the Utility Air Regulatory Group, UARG.

UARG is a not-for-profit association of individual electric generating companies and national trade associations. Since 1977, UARG has participated in many Clean Air Act administrative proceedings focused on electric generating companies and in the litigation arising from those proceedings.

Because electric generating companies have so often been targets of EPA rules, UARG members have substantial experience with the unnecessary burden and excessive cost associated with regulatory compliance. UARG therefore endorses the idea of EPA's modifying, replacing and repealing agencies' programs that are outdated or unnecessarily costly, complex or burdensome or impose costs that exceed program benefits.

UARG believes such changes can be made consistent with the requirements and goals of the Clean Air Act. UARG will be filing comprehensive comments by May 15th. Today though, we offered just a few comments on some of the regulatory programs that we believe EPA can and should address as it's about complying with Executive Order 13777.

First, UARG believes the Clean Power Plan and Carbon Dioxide New Source Performance Standards for new and modified and constructed -- reconstructed electric generating units are unlawful. UARG, therefore, supports EPA's already commenced review of these rules.

UARG believes that EPA's greenhouse gas reporting -- mandatory reporting program exceeds EPA's information gathering authority under the Clean Air Act. Facilities are now expending enormous resources, tracking, quality assuring and reporting vast amounts of information. EPA also continues to spend significant resources for both its own staff and agency contractors to implement the rule.

Since 2009, EPA has promulgated dozens of revisions to the GHG mandatory reporting program, although you are going to understand that many of these rule revisions have been directed at correcting errors or simplifying data collection and reporting the need with so many revisions underscores the already complicated nature of the program.

For the reasons pointed out in UARG's pending petition for partial reconsideration, EPA should reconsider and modify key aspects of the cross-state air pollution rule update for the 2008 Ozone Ambient Standards. That rule's serious flaws result in a new regulatory program that imposes cost in excess of any reasonable measure or projected benefits and it threatens jobs in the energy sector.

We also have suggestions for changing EPA's visibility program and the unnecessary cost and burdens of pre-construction permitting. We also recognize that members who spent billions of dollars complying with other Clean Air Act programs, and although most of this cost of compliance come from the purchase and installation and operation of controls, they also come from periodic performance testing, continuous emission monitoring, record keeping and reporting that are also costly.

We believe this can be avoided.

Andrea Drinkard: Thanks very much, Andrea. Your time is up.

Andrea Field: Thank you.

Andrea Drinkard: Operator, open the next line. Thank you.

Operator: Our next comment comes from the line of Charlie Jiang with the (Environment for) Defense Fund.

Charlie Jiang: Hi. My name is Charlie Jiang with Environmental Defense Fund. I am speaking on behalf of myself today.

As a young person, I will be (harmed) by the regulations EPA is attempting to roll back. EPA -- critical regulations that protect millions of Americans including (inaudible) health from the dangerous effects of air pollution.

I was lucky enough to grow up in a neighborhood that benefit from 45 years of EPA's common sense clean air protection. I was able to go to school every day to spend time outside with my friends and to receive an education and upbringing that enables me to be a productive American. But many of my peers across the country are having a different experience. They suffer from asthma, missed school because the air is too dirty for them to leave their house or have lost family members due to toxic air pollution.

It is crucial that we preserve and strengthen EPA's climate and clean air safeguards to ensure all Americans, regardless of race, geography, age or income can enjoy the benefits of a healthy, breathable atmosphere.

Any attempt to undo these so-called "burdensome regulations" are dangerous and that will only start to benefit wealthy executives while putting my life and those of millions of my fellow Americans in harm's way. I urge EPA to uphold and strengthen its critical clean air environment protection and listen to the large majority of Americans who support strong regulations that clean up the air we all breathe.

Thank you for the opportunity to comment today.

Andrea Drinkard: Thank you, Charlie.

Operator, would you open the next line please?

Operator: Our next comment comes from the line of Mandy Warner with Environmental Defense Fund.

Mandy Warner: Thank you. My name is Mandy Warner, and I am with Environmental Defense Fund. Today, however, I am speaking on behalf of myself and my family.

I have two daughters, ages four years and 11 months. I'm gravely concerned with actions EPA may take that would result in more pollution that can harm my children and millions of other children across the country.

I asked my four-year-old the other night why she thought clean air was important, and she said very simply, "So you can breathe." She's right, and that's what this stakeholder meeting should be all about -- ensuring clean air so kids can breathe.

We know from four and a half decades of environmental protection that the narrative of burdensome regulations is simply false. It's a narrative repeatedly disproven by industry's own actions to comply on time and more cheaply with standards reducing pollution for millions of Americans in the process.

There is an endless pool of worry parents have to contend with already. We worry about how much fish is safe for our children to eat every week to (inaudible) pollution, what days we need to be careful about letting our children play outside due to smoggy air, and what serious challenges our children will face from runaway climate change. And we rely upon EPA to set common sense safeguards to protect us from things we cannot protect our children from alone.

Please don't add to our worries by rolling back critical life-saving protections that can help ensure a healthier future for my children and children across America. Thank you.

Andrea Drinkard: Thank you, Mandy.

Operator, next line please?

Operator: And as a reminder, if you would like to make a comment, please press star-1 on your telephone keypad.

Our next comment comes from the line of Howard Feldman with American Petroleum Institute.

Howard Feldman: Good morning. Thank you, Sarah and Andrea.

API is the only national trade association representing all facets of the oil and natural gas industry, which supports 9.8 million U.S. jobs and 8 percent of the U.S. economy.

Record U.S. production refining is happening alongside greater environmental progress. CO2 emissions from power generation (advancing) near 30-year lows, thanks in large part to greater use of natural gas. Also cleaner burning transportation fuels and industry investments have reduced emissions of criteria pollutants. The oil and gas industry has succeeded despite the unprecedented level of federal regulatory actions targeting our industry.

Consistent with President Trump's stated objectives of American energy independence and economic growth, EPA and other federal agencies should embrace smart, cost-effective regulations while continuing to promote public health, safety and the environment.

API is preparing detailed written comments that I'd like to highlight three key air regulations. First, the 2016 oil and natural gas NSPS final rule, API submitted a detailed petition for administrative reconsideration of the final rule to Administrator McCarthy on August 2016. The previous 2012 standards developed in collaboration with industry along with industries incented to capture more of what we sell are already effectively reducing emissions.

We are encouraged by EPA's recent announcement to review the 2016 standards, and API supports a revision of those standards. Additionally, we urge EPA to act quickly to extend rapidly approaching compliance deadlines.

Secondly, there are a number of problems with the outdated RFS program. API recommends EPA should utilize its waiver authority to reduce the renewable fuel obligations to ensure the mandate does not exceed the E10 Blend Wall. In order to maintain a market for ethanol-free gasoline, EPA should not send an RFS mandate that would cause the average ethanol content to exceed 9.7 percent. EPA should reject cause to move the RFS point of obligation, and EPA should work with Congress to reform and ultimately end this unworkable program.

Moving to the Ozone NAAQS, API has commented previously that the more restrictive ozone standards imposed by EPA in late 2015 were unnecessary because ambient ozone levels were already declining under the 2008 standards, and the public health is already protected with an adequate margin of safety. Ozone levels will keep falling as the country works to fully implement the older standards and other federal regulations. Unfortunately, EPA's new standards create tremendous burden on states and risk significant impacts on job growth.

API supports EPA's reconsideration of the 2015 Ozone NAAQS based on the issues that API identified in its comments and corp briefs and is encouraged by EPA's motion to continue oral arguments on the 2015 Ozone NAAQS. It is difficult for states to harmonize activities towards the implementation of both -- the 2008 and 2015 NAAQS. Therefore, we'd encourage EPA to expeditiously complete its review.

In conclusion, we look forward to working with Administrator Pruitt, EPA leadership and staff on these and other rules. Regulatory action should be rooted in sound science and data with the consideration of the cost and benefits while protecting public health and the environment.

Andrea Drinkard: Thank you, Howard.

Operator, would you open the next line please?

Operator: Our next comment comes from the line of (Jerry Steffi) with Harley Davidson Motors.

(Jerry Steffi): Thank you very much. We appreciate the opportunity from EPA to comment on Executive Order 13777.

Our company has worked since the late 1970's closely with EPA on the development of motorcycle regulatory content, and we appreciate those relationships and dialogues.

Our comments today are more related to the processes and requirements related to on highway motorcycle certification, and that's foremost found in 40 CFR Part 86 sub Parts E and F around highway motorcycles.

We do believe that there are items that can be improved, modified or changed to reduce the burden on motor cycle manufacturers. In the first category, one item that Harley Davidson truly believes needs to be modified is that EPA gives consideration for the consolidation of the requirements and regulations that are presently found in multiple sources and therefore, causes undue burden on manufacturers.

Content with respect to motorcycle certification and requirements is found not only 40 CFR Part 86 but in many outdated advisories and guidances that are found at epa.gov and also in separate references found at EPA's website. This information by not being consolidated leads to excessive burden and extra time. In effect, we have heard from new manufacturers about how difficult it is to find information at particular times.

We also believe that there is a redundancy in EPA's informational requirements related to motorcycle certifications. When we consider the submittal processes on annual basis through EPA's CDX verify system, we find that we are giving the same information not only within EPA's database but in a separate section known as the upload compliance document section. An example of this specifically is the Tailpipe Emissions Data, which we requested to place in two different areas of the system. This redundancy is overly burdensome and leads to additional time that is not needed.

Also, we think EPA should consider removing the requirements for separate sets of Freedom of Information Act motorcycle submittals and files. We believe that they should be treated on a case by case basis and should not be created as a separate set of certification information on an annual basis. This leads to an undue burden in terms of the amount of time that's spent preparing regulatory documentation. This could be consolidated.

(Off-mic)

Andrea Drinkard: Your three minutes are up now. If you have…

(Jerry Steffi): OK.

Andrea Drinkard: …additional comments, remember you can submit them to the docket.

Operator, would you open the next line?

Operator: And your next question or next comment comes from Jeff Cooper with RFA.

Jeff Cooper: Well, good morning. My name is Jeff Cooper, and I am representing the Renewable Fuels Association, which is the (USF) and oil industry's trade association.

I first wanted to thank EPA for hosting this call. We agree that there are a number of EPA regulations that today offer little or no consumer protection or environmental benefit and are unnecessarily burdensome and costly for both producers and consumers of renewable fuels like ethanol. Specifically, we believe several of the fuel regulations under the purview of EPA's Office of Transportation and Air Quality are right for major reform and streamlining. We will be submitting detailed comments to the docket on specific regulatory provisions that warrant significant modification.

Today, however, I wanted to focus on perhaps the most egregious example of a burdensome and unnecessary fuel regulation that offers no environmental benefit and is actually increasing the cost of fuel for U.S. consumers.

I'm referring to EPA fuel rules that effectively prohibit the sale of gasoline containing 15 percent ethanol known as E15 in the summertime in most of the country. In essence, EPA has refused to apply the same volatility or RVP standard to E15 that it applies to today's marketplace gasoline, which is E10. And this is even though E15 is slightly less volatile than E10 and therefore results in fewer volatile emissions. EPA requires E15 to meet a volatility standard in the summertime that is 11 percent more restrictive than the standard apply to today's gasoline.

Due to this prohibition on selling E15, during the summer months, most retail gas stations have chosen not to offer the fuel even though it is cheaper and a cleaner alternative with a higher octane rating. We believe this EPA-imposed market dysfunction can be corrected with simple administrative action. We believe EPA should level the playing field for E15 and today's E10 gasoline with respect to fuel volatility.

EPA could accomplish this by immediately extending the current E10 volatility standard to all ethanol blends including E15 or it could immediately lower the volatility limits for gasoline blend stock such that all finished ethanol blends would meet current gasoline volatility standards. While the E15 RVP barrier is our industry's most important regulatory barrier in the near-term, it is symptomatic of larger problems with our current fuel regulatory framework, and we look forward to submitting more detailed comments on some of those other provisions.

Lastly, I want to voice our strong support for the renewable fuel standard. I want to respond to the comment from API that we have an issue with the so-called "blend wall." In fact, ethanol content of gasoline last year already surpassed 10 percent well above the 9.7 percent safeguard that API is promoting. So I just wanted to make sure that it gets in the record that the blend wall is a fiction and should not be a consideration for EPA's rulemaking process on the RFS.

Thank you.

Andrea Drinkard: Yes. Thank you very much, Jeff.

Operator, next line please?

Operator: And your next comment comes from (Andrew Wilson).

(Andrew Wilson): Hi. My name is (Andrew Wilson). I am speaking on behalf of myself and about the EPA regulatory process.

In July of 2015, I went to Atlanta, Georgia, and testified on behalf of -- in favor of the Clean Power Plan. I was incredibly in favor of it then and saw the robust public process firsthand that happened over two conference rooms full all day long, people all day speaking on behalf of the EPA taking action on climate change responsibly. And out of that process came a very robust and very responsible regulation, and now we're being asked to roll it back.

In January of 2015, here in Austin where I live, I attended an EPA public hearing on the ozone -- or on the regional haze standard and there testified on behalf of myself and my children who go out and enjoyed Big Bend National Park that the regional haze problem is something that EPA needs to step in on and have more robust regulation of. And now we're being asked to roll that back. No, absolutely not.

And just two weeks later, in Arlington, I testified again on the Ozone Standard. And again all day long, people were testifying saying, "This is important. This is my air that we breathe. These are my children. Our air quality is negatively impacted, and EPA needs to act on that."

And I will repeat what I testified there then that I lost a friend. His name was (Jess). And (Jess) died of a massive asthma attack. And he lived in Salt Lake City, Utah. And on the day when he died, the ozone level in the air was at about 70 parts per million. We need to go further because every time we talk about rolling back the regulation, these are people's lives. These are my children's lives. This is our future on the planet, and we cannot move backwards on that, and we need to have a strong, robust process at least as robust as what we had in the past.

Thank you for your time.

Andrea Drinkard: Thank you, Andrew.

Operator, next comment.

Operator: Your next comment comes from the line of Ben Klein with Uranium Producers.

Ben Klein: Hi, thank you. I appreciate the opportunity to speak. On behalf of the Uranium Producers of America, I wanted to speak today for a few minutes about a rule that was initially proposed in January 2015, the Health and Environmental Protection Standards for Uranium and Thorium Mill Tailings.

Basically, the rule would require in situ uranium mine operators to conduct long-term monitoring among a number of other new requirements. And at the time the rule was initially proposed, EPA provided no justification for the rule, we felt they felt account for the cost. They didn't consider the small business impact. They also didn't follow a number of recommendations from their Science Advisory Board.

The EPA is acknowledged on a number of occasions. They're not aware of a single example of an ISR uranium project contaminating groundwater at an adjacent non-exempt aquifer. And the EPA has also acknowledged that they really didn't consult with the industry or state regulators, including Texas Commission on Environmental Quality who's been regulating the industry for more than three decades.

TCQ offered to work with the EPA. They offered to provide additional groundwater data. They offered to even conduct additional sampling if EPA had concerns about groundwater quality around current or historic uranium projects.

EPA has proposed a rule well beyond the agency's authority. This is a concern that was raised by the Nuclear Regulatory Commission who's really the primary regulator in this space.

We were pleased that EPA decided to withdraw the proposed rule on December 2016. However, the agency issued a new version of the proposed rule that is nearly identical on January 19th, so the last day of the last administration.

The new rule equally troubling, again there's no evidence to justify it in the docket. Nothing -- EPA doesn't consider any of the peer reviewed science that's out there. And essentially if the rule is finalized, it would make ISR uranium mining completely unattractive from a cost standpoint, and we'd see most of the ISR uranium projects.

And in the U.S., in a time when we're importing 94 percent of the uranium needed for our nuclear reactors, which provides 20 percent of our electricity, it seems the administration should be working with the industry to strengthen our domestic uranium mining rather than -- rather than pursuing the regulation that would eventually put the industry out of business. And so we know this is just a proposed rule, but it's up and it's generating considerable uncertainty. It's making it harder for companies to go out and raise capital. And so we're asking EPA to immediately withdraw the proposed rule and work with the industry as we go forward.

Thank you for your time.

Andrea Drinkard: Thank you, Ben.

Sorry, operator, could you open the next line?

Operator: And your next comment comes from the line of Joseph Stanko with the NAAQS Implementation Coalition.

Joseph Stanko: Thank you. I am counsel to the NAAQS Implementation Coalition, which includes trade associations, companies and other entities who confront

challenges in permitting and operating facilities under increasingly stringent National Ambient Air Quality Standards.

Our diverse membership reflects the impact that NAAQS implementation challenges have across the American economy. That is why addressing these challenges to create a reasonable path towards project development is critical to fostering economic expansion that creates well paying jobs and generates needed tax revenue to local communities throughout the country.

The Clean Air Act requires that those seeking to build or expand major facilities in attainment areas first provide prevention of significant deterioration PSD permits from EPA that demonstrate the permit project will not excessively degrade air quality. PSD permit applications make such demonstrations to remodeling using EPA approved tools and policies. However, the multiple layers of conservatism that EPA has historically built into these tools and policies have long been known to significantly overpredict the impacts.

Prior to recent changes to the NAAQS for NO2, SO2, PM2.5 and Ozone, there were sufficient headroom between NAAQS and facility emissions plus the ambient background that impacts from other sources such as this conservatism was not generally problematic.

With those margins, shrinking or disappearing is more stringent NAAQS approach background levels, our members are finding that overprediction resulting from these conservative tools and policies can be a significant even determining factor in project permitting demonstrations.

We believe EPA can implement a number of measures to improve NAAQS implementation tools and policies. This include updating preferred model performance of low wind speeds, eliminating overly burdensome photochemical grid modeling requirements for single sources and updating emission factors. Such improvements fit squarely within the regulatory review called for by E.O. 13777.

For example, under the category of eliminating jobs or inhibit job creation, overpredictions from NAAQS implementation tools and policies result in modeled air quality impacts that do not exist. These modeling glitches can effectively prevent a needed permit for closing projects.

In the category of outdated, unnecessary or ineffective, NAAQS implementation tools and policies, some of which have been overtaken by the agency's increasingly more stringent standards, EPA should update its outdated tools and policies to confront new NAAQS implementation challenges. Impose cost that exceed benefits, NAAQS implementation challenges are even inhibiting projects that would reduce emissions and then the category of inconsistent with regulatory reform initiatives, NAAQS implementation challenges have been identified in the Department of Commerce's manufacturing burden and request implementation.

We will be submitting comments for the record and appreciate the opportunity to address EPA. Thank you.

Andrea Drinkard: Thank you, Joe.

Operator, next comment please?

Operator: And your next comment comes from Rhett Cash with American Coatings.

Rhett Cash: My name is Rhett Cash, and I work for the American Coatings Association. ACA is a voluntary nonprofit trade association working as an advocate, an ally to advance the needs of the pain and coatings industry and the professionals who work in it.

ACA has flagged the following EPA regulations that could be repealed, replaced or modified to make them less burdensome without impacting the level of protection to the environment or the health and safety of our citizens.

First, ACA requests that EPA update its aerosol coatings regulations found in 40 CFR Part 59 sub Part E. Specifically, ACA requests that EPA update its reactivity values, adjusted default value, modify its regulatory language to

allow for changing the value of existing compounds and add new compounds to its tables. Our member companies are especially burdened by EPA's current aerosol coatings regulations because they are no longer consistent with the regulation found throughout the country especially California, which is the leader in aerosol and coatings regulations and who updated its rules in 2010.

EPA's current regulations mirror California's old regulation and need to be updated. Our proposed updates would promote uniformity in aerosol and coatings regulations throughout the country and reflect the most recent scientific research available.

Second, ACA requests that EPA eliminate its tri-annual reporting requirements for aerosol coatings. These requirements are not only burdensome and costly for industry, but also provide little, if any, useful value or information to EPA. If there are compliance issues, this information can be requested by the agency, and manufacturers would then be required to provide it. Clearly, the burden outweighs the benefit.

Third, ACA urges EPA to revert to the 2008 National Ozone Standard of 0.75 parts per million. In 2015, EPA lowered the National Ozone Standard from 0.75 ppm to 0.70 ppm. The lowering of the standard now require states to identify whether they are in attainment or non-attainment. If they are non-attainment, then those states must revise their state implementation plans and develop even stricter VOC emissions regulations. This change will be very costly on the coatings industry because it will limit business expansion and impair the ability of U.S. companies to create new jobs.

The high cost of this change outweigh the commensurate benefits to public health in the environment. Thus, ACA urges EPA to revert to the 2008 Ozone Standard and fully implement the standard so that the forward progress already achieved under it can be extended without unnecessarily burdening of the coatings industry.

Lastly , ACA requests that EPA amend the Clean Air Act regulations so that they extend the time for review of the Ozone Standard to every 10 years

instead of every five years to allow for more stability in the marketplace for formulators also protecting human health and the environment.

Thank you for the opportunity to discuss these regulations with u. We look forward to discussing and working with you and your regulatory reform efforts in the future. Thanks.

Andrea Drinkard: Thank you very much, Rhett.

Operator, would you open the next line please?

Operator: Certainly. As a reminder, to ask -- to make a comment, please press star-1 on your telephone keypad.

Our next comment comes from the line of Ben Henneke with Clean Air Action Corporation.

Ben Henneke: Good morning. This is Ben Henneke. I am president of Clean Air Action Corporation, a company that has been involved with reducing regulatory cost for over 25 years. I was appointed by President George H.W. Bush as a charter member of the Clean Air Act Advisory Committee and was appointed by each president then after. I served on that Advisory Committee until 2009. For over a decade, I was the co-chair of the Economic Incentives and Regulatory Innovation Subcommittee.

There are many existing EPA air and radiation regulations that put the burden of unnecessary cost and delays on the American people. Those delays and unnecessary cost harm America. Pollution also harms America through unnecessary sicknesses, medical cost, loss of productivity, decreased soil and water quality, and reduced land productivity.

The challenge for EPA is to reduce burdens from regulations and also reduce cost and burdens from the pollutants. If EPA air and radiation is able to accomplish this challenge, it will set a good example for other federal agencies and other EPA programs. To reduce both cost and pollution is not

actually difficult. I will outline three simple levels of increasing complexity and administrations effort that will accomplish this dual challenge.

At the simplest level, the EPA can provide state, tribal and local enforcement flexibility on a case by case basis. The requirements for a source or a manufacturer of pollution creating products to request the enforcement flexibility would be showing that using the alternative compliance approach would increase pollution reductions, accomplish them sooner than regulatory compliance would and, of course, reduce cost.

The source using that alternative would also provide public report to their emissions and the results of their alternative compliance.

The next level of complexity would be for the EPA to publish guidance to the states, tribal and local permitting and compliance agencies of formal trading mechanisms that would allow any source to use reductions beyond regulatory requirements that are made in the geographically (inaudible) areas. That type of mechanism will encourage early reduction solution, provide sources with a broad range of emission reductions that they can use to meet requirements.

The guidance would deal directly with local effects as well as assuring transparency on the creation (of) emissions reductions. Development of guidance should allow local flexibility to create improve approaches that are then included in regular new guidance. The guidance should require that the implementing agency would show the pollution reduction, existing regulations that the reductions would occur more rapidly and that both cost and delays would be reduced.

The greatest level of complexity but also the greatest benefits the environment and jobs throughout the nation, EPA would review existing regulations and any future regulations to determine what alternative methods pollution reductions for compliance exist or can be reasonably expected to become available within the next three years. This approach would allow sources, both stationary and mobile, to focus on the pollution reductions needed and be able to plan…

Andrea Drinkard: Thank you, Ben, for your comments. Your time is up. If you have additional comments, you can, of course, submit them to the docket.

Ben Henneke: Thank you.

Andrea Drinkard: Operator, would you open the next -- would you open the next line please?

Operator: Our next comment comes from the line of (Norbert Rigby).

(Norbert Rigby): Good morning. I am a non-governmental organization of one. I am going to address a radiation regulatory reform, and I would like the EPA to consider carefully a 2015 petition before the NRC Docket ID NRC2015-0057.

My comments on this are as follows. Discard and disavow the no-threshold hypothesis because it is not based on evidence, but has been a fraud from the start as Edward Calabrese documented at least in 2011, '13 and '15.

Discard and disavow the ALARA principle. It makes no sense in light of the huge temporal and spatial variability of background to those on planet Earth without any evidence of harm or risk resulting from the high end of that range.

Discard and disavow the concept of collective dose. It never made sense and no evidence exists to support its application.

Declare below regulatory concern, any chronic exposures below at least 250 millisievert or 25 REM per year. This is approximately the largely agreed upon chronic dose to some inhabitants of Ramsar in Iran, which is the highest currently known background location on planet Earth. Without any evidence of harm or risk caused by that dose, this limit may need to be erased as additional reliable information is obtained. They often suggest that limit of 100 millisievert or 10 REM is an arbitrary number plucked more or less from thin air. In summation, EPA must base regulations on observable evidence not on unsupported assumptions, projections and models.

Thank you for taking my comment.

Andrea Drinkard: Thank you very much, (Norbert).

Operator, next comment please?

Operator: Our next comment comes from the line of Tim Hogan with American Fuel.

Tim Hogan: I'm Tim Hogan, director, Motor Fuels at the American Fuel and Petrochemical Manufacturers. AFPM is a national trade association representing nearly 400 companies that encompass virtually all U.S. refining and petrochemical manufacturing capacity.

I will briefly cover three regulations we believe are the most burdensome for our member companies. The first is RFS. AFPM opposes government-mandated biofuel blending which distorts the free markets' efficient allocation of transportation fuels and disadvantages consumers.

The statute contains an aggressive schedule for renewable fuel blending. Declining gasoline demand and higher ethanol mandates threaten our nation's fuel supply. EPA must use realistic projections and continue to exercise this waiver authority to reduce some noble fuel obligations in recognition of the E10 blend wall. Just moving beyond the blend wall is not feasible for the existing fleet of motor vehicles, small engines and the field distribution infrastructure.

To ensure a playing field between refiners and large-exempt blenders, EPA must move the point of obligation to the position holder at the rack. The new Ozone Standard of 70 ppb increases the (inaudible) non-attainment areas due to background ozone levels, making it increasingly difficult to permit new facilities or modify existing facilities in these areas. In this regard, the current five-year review cycle for NAAQS does not provide enough opportunity for full implementation of preexisting NAAQS.

The administration can ease the burden by seeking to realign non-attainment designations for the 2015 Ozone NAAQS to 2025 to allow for full implementation of the 2008 Ozone NAAQS and other federal and state rules that will continue to reduce ozone information. Neither the 2008 review nor

the more recent ozone studies justify lowering the standard based on the health effects of exposure, therefore, EPA -- therefore, the administration should take steps to increase the quality of data EPA replace upon for NAAQS rulemakings.

Finally, AFPM has concerns about EPA's refinery executive rule, which poses significant cost to industry and the economy with little or no health or environmental benefits.

AFPM supports EPA's process to evaluate the residual risk remaining after full implementation of refinery MACT rules. However, we do not support EPA's implementation of standards applicable to periods of startup (strapped down) and malfunction, the plain provisions of the rule or the new fenceline monitoring regulations, all of which impose significant compliance cost despite EPA is now showing very low levels of risk.

We urge EPA to act on pending petition for reconsideration and to reject petition for reconsideration filed by various environmental groups challenging the work practice standards for pressure relief devices and emergency flaring.

Thank you for this opportunity.

Andrea Drinkard: Thank you very much, Tim.

Operator, if you could open the next line please.

Operator: Our next comment comes from the line of Paul Noe with the American Forest and Paper Association.

Paul Noe: Thank you and good afternoon. I am the vice president for Public Policy at AF&PA. AF&PA serves to advance the sustainable U.S. pulp, paper packaging, tissue and wood products manufacturing industry through a fact-based public policy and marketplace advocacy.

The forest products industry accounts for about 4 percent of U.S. manufacturing GDP, manufactures over $200 billion in products annually and

employs about 900,000 hardworking men and women often in small rural communities.

Today I want to call your attention to a very long-standing rulemaking that's been 25 years in the making -- EPA's Boiler MACT Rules. This rulemaking was about completed by the last administration, but unfortunately faced the court, remand in July of 2016. The court vacated certain limits in the rule. And now EPA has to complete the job and get this rule put to bed.

We would ask that the agency get a proposed Boiler MACT Rule out within six months to recalculate the few remaining limits that need to be done pursuant to the court. And that this is important for regulatory certainty and to finally close the chapter on this rulemaking, which is I said has been over 25 years in the making.

Thank you.

Andrea Drinkard: Thank you, Paul.

Operator, could you open the next line please?

Operator: Our next comment comes from the line of Leila Ghaznavi with Carnegie Hall.

Leila Ghaznavi: Hello. I am writing to strongly or calling to strongly endorse the EPA's current regulations. I grew up at Pittsburgh, Pennsylvania, a state that has been the heart of the steel industry.

Before the EPA, the -- is completely unlivable. People had to wear one set of clothes to work and carry their work clothes work with them in a bag because the soot that was in the air would coat their clothes before they ever made it to their desk.

Asthma and other breathing-related issues were a significant health issue for the entire city. Even today, the enactment of the EPA major clean efforts for the city, you can still see the building staying black from the soot of those factories. And while that soot is a (marker pride) of our industrial roots, it is

also a visible reminder of the importance and the impact that the EPA has had on the health and wellbeing of the city.

Pittsburgh is now considered one of the most livable cities in the nation, a far cry from its poor regard in the 60's and 70's. This evolution would not have happened without the EPA.

And for those who would say that Pittsburgh has suffered from the change and evolution of the steel industry, I will counter that EPA did not damage the steel industry by requiring factories to reduce their emissions. It was the investment of technology in Japanese steel. Our lack of investment in U.S. technology combined with the reliance on import taxes to (dull) competition for American steel in the U.S. that ultimately hobbled Pittsburgh steel industry.

Today, Pittsburgh is a thriving city with a sound economic base and technology and a center for healthcare innovation. I am thankful to the EPA that the fact that my niece and nephew will grow up in Pittsburgh never seeing a city sunrise and can go to school in the same clothes that they left their homes in.

The EPA has had a profound and an important impact on the health and wellbeing of Americans. I strongly oppose any effort to reduce minimize or negate the effectiveness of its important work. Thank you very much.

Andrea Drinkard: Thank you, Leila.

Operator, if you can open the next line please?

Operator: Our next comment comes from the line of Christine Pratt with Seattle City Light.

(Off-mic)

Kate Engel: Hello. This is actually Kate Engel with Seattle City Light. Can you hear me?

Andrea Drinkard: Yes, we can hear you. Go ahead. Kate?

Kate Engel: Oops. Seattle City Light provides electricity to Seattle's residential, commercial and industrial customers by generating 90 percent of energy through hydroelectric operations.

The impacts of climate change on mountain snowpack and glaciers that supply much of the water for our projects poses a threat to Seattle and the region's ability to continue to prosper in the coming years.

The effects of climate change have already been felt. In a warning climate, extreme events like storms, floods, droughts, wildfires, landslides and longer, more intense heat waves are likely to become more frequent. These changes threaten the snowpack and river flows that we depend on as well as on Seattle City Light's infrastructure and operations.

We have supported EPA's work on climate change and written an oral comments including the support of the endangerment findings, the greenhouse gas, tailoring rule, the Clean Power Plan and other proposed regulations for new and existing electric power plants. We maintain our position and believe that addressing climate change through regulating emissions of greenhouse gases is an urgent and vitally important action.

The city of Seattle and Seattle City Light have been long time advocates for federal action on climate change. We believe the EPA should continue the work of addressing climate change through the Office of Air and Radiation given the compelling scientific findings and evidence of climate change already occurring.

Thank you.

Andrea Drinkard: Thank you, Kate.

Operator, could you open the next line please?

Operator: Our next comment comes from the line of James Enstrom.

James Enstrom: Hello. My name is Dr. James E. Enstrom. I have a doctoral level training in both physics and the epidemiology, and for the past 44 years I have conducted high-quality peer-reviewed epidemiologic research at UCLA. I am asking EPA to reassess and modify the National Ambient Air Quality Standard for fine particulate matter.

On March 28th, I published a major peer-reviewed article showing that PM2.5 is not related to total mortality or premature deaths in the United States. This null relationship, which is on based on my analysis of the large 1982 American Cancer Society Cancer Prevention Study cohort, contradicts the positive relationship in the same cohort that was published in 1995 by Pope. And that was the primary justification for the establishment of the PM2.5 NOX by EPA in 1997.

The difference in findings occurred because the 1995 Pope analysis used inferior PM2.5 measurements and used only a selected portion of the available ACS data. My findings are also supported by the null findings in a 2016 article that analyzed the large National NIH AARP cohort.

My independent analysis of the otherwise still secret ACS data demonstrates the importance of basing EPA regulations on transparent and reproducible science as required by the HONEST Act. H.R. 1340 has been approved by the House of Representatives and is awaiting action in the Senate.

Since March 10th, I have requested that Pope, Krewski and the Health Effects Institute confirm my null findings, and they have provided no evidence that my findings are incorrect. Thus, EPA must immediately reassess the validity of the PM2.5 NOX and all regulations such as the Clean Power Plan that are justified by alleged PM2.5-related premature deaths.

The initial focus must be on my new findings on the apparently incorrect findings of Pope, Krewski and HEI and on the extensive evidence that healthy levels of PM2.5 have already been achieved in America. EPA must not approve any further (inaudible) waivers, state implementation plans or air quality management plans until this PM2.5 NOX reassessment has been made.

Thank you very much for your consideration. I will be submitting written comments to supplement these verbal comments.

Andrea Drinkard: Thank you very much, James.

Operator, would you open the next line please?

Operator: Our next comment comes from the line of Giedrius Ambrozaitis with Alliance of Auto Manufacturers.

Giedrius Ambrozaitis: Yes, hello. My name is Giedrius Ambrozaitis. I am speaking on behalf of the Alliance of Automobile Manufacturers. The Auto Alliance is a trade association that represents the interest of the 12 largest automobile manufacturers in the United States, representing 70 percent of all car and light truck sales in the United States. Thank you for the opportunity to speak today.

On this call, we would like to state that the alliance appreciates further opportunity to provide input on President Trump's Executive Order 13777 and how the Office of Air and Radiation can review, repeal, replace and modify regulations to make them less burdensome.

We are looking forward to submitting our written comments to the docket. Thank you very much.

Andrea Drinkard: Thank you, Giedrius.

Operator, if you could open the next line please?

Operator: Our next comment comes from the line of Aminah Zaghab with Environment America.

Aminah Zaghab: Hello. Thank you for this opportunity. My name is Aminah Zaghab, and I am with Environment America, a federation of 29 state-based environmental organizations working for clean air, clean water and open space.

On that note, we are very concerned with potential rollbacks to our EPA protections, climate safeguards, protect our health, conserve our resources and save lives with benefits that far exceed the cost of compliance year after year.

The Clean Air Act alone prevents more than 160,000 premature deaths and 1.7 million asthma attacks every year, delivering up to $90 in public benefits for every dollar invested in clean air. In particular, we're very concerned with the tax to the Clear Power Plan and the Clean Car Standards.

The EPA's Clean Power Plan represents the most significant steps the U.S. has taken to address the urgent threat of climate change. And the EPA's Clean Cars and Trucks Standards are essential for protecting public health and the environment. In fact, the Clean Car and Fuel Economy Standards currently in place are second to none in terms of policies that reduce transportation carbon pollution, our current top emitter, and reduce our dependence on costly oil.

In fact, the EPA reports that the Car Greenhouse Gas Standards in place through just 2012 have already avoided 160 metric tons of carbon pollution while at the same time saving consumers over $35 billion at the gas pump. This is the progress that we need to continue rather than weaken.

Thank you very much for this opportunity. And we hope to see these standards protected.

Andrea Drinkard: Thank you, Aminah.

Operator, would you open the next line please?

Operator: Certainly. Our next comment comes from the line of Henry Frey with North Carolina State.

Henry Frey: Thank you. I'm speaking as a private citizen. EPA is required under the Clean Air Act to develop and implement standards and cannot simply repeal them. The setting of emission standards where there's New Source Performance Standards, National Emissions Standards for Hazardous Air

Pollutants, Mobile Source Standards, et cetera, entails usually a lengthy rulemaking process with technical support documents, public comment, EPA response to comment and, in many cases, also a regulatory impact analysis that assesses benefits and cost.

So these are deliberative processes. They are generally not arbitrary and capricious.

With regard to the Clean Power Plan, EPA is obligated to act as a result of an endangerment finding some years ago that's based on scientific evidence of adverse effects of greenhouse gas emissions. EPA cannot simply disregard that endangerment finding and is obligated to take action under the Clean Air Act. The existing standards having been promulgated with regard to a lawful process cannot simply be set aside, and to do so arbitrarily and capriciously would invite tremendous number of lawsuits.

I'll also comment on the National Ambient Air Quality Standards that several commenters have talked about. EPA is required to set health protective standards, but the language in the Clean Air Act is they must protect public health with an adequate margin of safety and that the standards must be science-based and reviewed every five years.

According to a 2001 Supreme Court case, it is simply illegal for EPA to consider cost and technical feasibility of attaining a NAAQS when setting the NAAQS. So the NAAQS are really the only standard in the U.S. that is purely based on public health.

EPA is required to have an external body of experts, review the scientific basis of the NAAQS and so the NAAQS process is explicitly science-based. And in contrast to some of the comments we've heard, those rulemakings do not rely on a single study. They rely on the overall weight of evidence of the body of scientific literature, not a single study. For example, the revised Ozone Act, which some people are calling for setting aside, cannot simply be undone without a science-based rulemaking process. And for two revision cycles of the Ozone standard, the Clean Air Scientific Advisory Committee

has advised the administrator that the standard is not protective of public health unless set at levels in the 60 to 70 ppb range.

So furthermore, the effectiveness of existing emission regulations, which some commenters had pointed out, means it will become easier to attain the Ozone NAAQS.

And very briefly, I just want to emphasize that environmental regulations do not kill jobs. They may redistribute benefits and cost, but they don't lead to a net reduction in employment. And as others have pointed out, we've had tremendous economic growth since 1970 when the EPA was formed.

Andrea Drinkard: Operator, would you…

(Crosstalk)

Andrea Drinkard: …line please?

Henry Frey: …the benefits of the Clean Air…

Operator: Our next comment comes from the line of Ron Sober with RFS Consulting Inc.

Ron Sober: My name is Ron Sober. I'm a licensed environmental engineer and president of RFS Consulting, Inc. We're a small independent environmental engineering and consulting company, which assists sort of the industries and permitting compliance, recordkeeping reporting regarding the environmental rules and have over the past 40 years.

In this effort, I'm immersed in rules and regulations, some of which makes sense and some of which do not. As such, I'd like to offer the following comments on a handful of regulations or policies, which deserve reconsideration or modification.

40 CFR Part 98, pertaining to greenhouse gas emission reporting, no underlying rule or standard or limit governing reported emissions. We're

talking about non-criteria pollutants, non-regulated pollutants not required by the Clean Air Act of 1990 with no clear purpose for data being generated. This imposes a significant cost of regulated community for which there is no tangible benefit while not overly cumbersome to some industry sectors or equipment.

Sub Part W specifically pointed to the oil and gas industry imposes significant burden, which this industry type has multiple pieces of equipment, which must be tracked, monitored, data compiled just to determine if reporting threshold is triggered. This effort results in a significant financial burden whether reporting is required or not.

Second point is related to 40 CFR Part 63 MACT Standard in the "Once in, always in" policy. This policy by itself undermines any incentive to reduce emissions of hazardous air pollutants to below a trigger point and creates an unnecessary burden on continued compliance. There's no incentive to accept restrictions or modify operations to become a synthetic miner source. And the policy itself creates a burden on those desiring to reduce hazardous air pollutants since there is no benefit in doing so. The burden of reporting continues indefinitely with the cost being reported, generated and submitted to the regulatory agency only in, always in policy.

I have other comments. My time is up. I will be submitting written comments in the docket. Thank you.

Andrea Drinkard: Thank you very much, Ron.

Operator, would you open the next line please?

Operator: Our next -- our next comment comes from the line of (Don Giardinni) with Equipment Company and (Cardinal Manufacturer).

(Don Giardinni): Thank you very much. My name is (Don Giardinni). I'm one of the designated EPA Compliance team members with (Cardinal Manufacturing). It's an engineering with (higher equipment) company (inaudible) engine distribution.

My comment is regarding 40 CFR Part 1060.1 through 1060.825, control of evaporative emissions from new and end-use non-road and stationary equipment specifically with category engines defined in 40 CFR Part 1054, control of emissions from new small non-road spark ignition engines and equipment, which specifically designates the N.S. in our S.I. category as the spark ignited engines with a maximum engine power at or below 19 kilowatts.

I asked the Task Force to consider these evaporative emissions regulations as (ineffective) and take appropriate actions directed by this Executive Order. The logic is the permeation standards for fuel tanks and fuel lines, as dictated, represent a very, very small amount of vapor escaping into the environment through the walls of the fuel tank and fuel lines. This specify them out of 1.5 grams per square meter per day is so small, in fact, specialized equipment is needed to measure.

When this small amount of vapor that permeate through the walls of these components is considered versus the amount of vapor that escapes into the atmosphere, every time the fuel cap is removed to check how much gas is in the small equipment's tank or the cap is removed to fill up the tank, a realistic perspective appears. Several thousand days' worth of this limit is released into the environment each and every time the fuel cap is removed from the tank. Hence, the environment has been protected from nothing. This extremely small amount of vapor has simply been saved in the tank to be released when the fuel cap is removed.

Because the equipment covered here is largely small water pumps, generators, lawn mowers and all the typical small engine powered machines of the world with typically small fuel tanks, I believe if the Task Force considers how they are used in the field and how many times the gas cap is removed, (that then) evaporative emissions is attained by these regulations. This is capable logic, cannot be denied. Therefore, making these evaporative emissions are attractive.

So the burden of the manufacturer to obtain the certificate of compliance, pay the fees, pay the fines when the record keeping is correct and increase the products price in the market to absorb the expense is especially great whether one considers no net gain for the environment is actually attained.

Thank you very much for the opportunity to comment.

Andrea Drinkard: Thank you very much, (Don).

Operator, next line please?

Operator: Our next comment comes from the line of Jerry Hiatt with Nuclear Energy Institute.

Susan Mathiascheck: Hello, this is Susan Mathiascheck. I'm speaking on behalf of NEI, the Nuclear Energy Institute.

Nuclear energy provides by far the largest share of emissions-free electricity in the U.S. today. On behalf of the Nuclear Energy and our other members, NEI appreciates the opportunity to comment on EPA's regulatory review under the Executive Order and supports the agency's effort to examine its regulations and to maintain protection of human health and the environment going forward.

To that end, NEI will be submitting more detailed comments for the docket by May 15th. Thank you.

Andrea Drinkard: Thank you.

Operator, next line please?

Operator: Our next comment comes from the line of Nathaniel Burden with Fidelity.

Female: One second.

Operator: Fidelity Inspections.

Andrea Drinkard: Nathaniel, your line is open. We can -- we -- do you have a comment?

(Off-mic)

Andrea Drinkard: You may be on mute. We can't -- we can't hear you.

All right. Operator, if you'd open the next line please?

Operator: Our next comment comes from the line of Don Hancock with Southwest Research.

Don Hancock: Hello. Southwest Research and Information Center is a private nonprofit organization primarily involved with ARIA's work regarding the Atomic Energy Act and the WIPP Land Withdrawal Act. We also recognize the essential public health and economic benefits of ARIA's regulations related to clean air. We're also very much involved and concerned about public participation and information in the rulemaking process.

Executive Order 13777 that we're discussing today is the result of and a progeny of Executive Order 13777. That Executive Order Section 3A states that each agency's best approximation of the total cost or savings associated with each new regulation or repealed regulation is required.

Our concerns are that the cost calculations should include quantifying the health effects on existing populations of new and modified or repealed regulations. The cost calculation should include the cost and benefits to President Trump and his family's businesses and other related costs.

The Regulatory Reform Task Force that EPA has should also be identifying regulations that haven't been issued or not enforced that are required by existing law, not just new or existing regulations.

Furthermore, in terms of public transparency, the cost of the regulatory task force should be publicly disclosed and all of the reports of the regulatory task force should be publicly available on the EPA and ARIA's websites. Thank you.

Andrea Drinkard: Thank you, Don.

Operator, would you open the next line please?

Operator: Our next comment comes from the line of Nadia Steinzor with Earthworks.

Nadia Steinzor: Yes, hello. I am speaking on behalf of Earthworks, a nonprofit organization that focuses on oil and gas issues and protecting communities from the negative impacts of those industries.

I speak today both as someone with asthma and as a researcher who has documented the air pollution and health impacts caused by the oil and gas industry and how communities pay the price with their health, quality of life and property values.

A growing body of scientific evidence demonstrates these facts, including through 100s of peer reviewed studies. Nothing should be done to roll back the new federal rules to control oil and gas air pollution finalized under President Obama.

The U.S. uses over $1 billion worth of natural gas every year through methane leaks and intentional releases throughout the oil and gas system. This is enough natural gas to meet the heating and cooking needs of over 5 million American homes. These common sense regulations that have been put in place after painstaking and lengthy public review and comment would solve this problem.

Methane pollution is a grave threat to global climate and to air quality and health. Methane emissions caused pollution hitchhikers as well, stemming leaks and releases of methane with lower emissions of pollutions like nitrogen oxides which form ozone and smog and harm health.

Data clearly show that its oil and gas operations have expanded so to have the pollution it caused. Several years into the shale gas and oil boom, the Obama administration realized that it was high time for change.

Any attempted rollbacks by the Trump administration would fly in the face of this extensive public and scientifically based process and would be nothing less than payoff to oil and gas corporations for their financial support during the election, and (the vast) upfront to the public. Thank you very much, and we will submit written comments as well.

Andrea Drinkard: Thank you very much, Nadia. Operator, would you open the next line, please?

Operator: Yes. Our next comment comes from the line of Vince Brisini with Olympus Power.

Vince Brisini: Thank you. It's very important for EPA to reconsider repetitive regulatory obligations and onerous and excessive testing monitoring and reporting requirements that only serve to add unnecessary cost.

Also, in establishing regulatory obligation, EPA needs to use the most current and the best available information rather than relying upon outdated emissions inventories that result in inflated representations of impacts and benefits.

And benefits should not be double counted between regulations by considering them independently. EPA and other regulators cannot rely upon conjecture when representing environmental impacts. It appears to be occurring in a recent draft regional haze report for the Northeast.

So, the important facts to consider are, for example, the 43 of the 50 ozone monitors in Pennsylvania have already measured attainment of the 2015 standard using the 2014 through 2016 data.

And this is occurring prior to Pennsylvania, Reasonably Available Control Technology 2, the national mobile source NOx reductions from the implementation of tier 3 gasoline and implementation of the ozone season nitrogen oxide Cross-State Air Pollution Rule update, all of which became effective in 2017.

Nationally, some of the electric generating unit emissions reductions that have occurred between 2002 and 2016 are an 85.4 percent reduction in sulfur dioxide, 72.8 percent reduction in annual nitrogen oxide emissions, a 70.2 percent in ozone season nitrogen oxide emissions and a 74.7 percent reduction in non-ozone season emissions. Thank you for the opportunity to make this statement.

Andrea Drinkard: Thank you very much, Vince. Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Gloria Linnertz with Citizen For Radioactive Radon Reduction

Gloria Linnertz: Hello. My name is Gloria, and I am President and Founder of Citizens for Radioactive Radon Reduction. The drastic act of removing the funding for the State Indoor Radon Grant and cutting the EPA radon program would take the lives of American people.

A few people know about the invisible killer that maybe in their home schools or workplaces but the discontinuance of the outreach efforts of the state radon programs no one will know. And that elevated levels of radioactive radon gas have been found in every state and in our nation including yours.

There is no federal or state law that requires radon testing at the time of the home that's purchased therefore many people were never aware that they've been living with this silent killer in their schools and homes and work places until they are diagnosed with lung cancer.

How can our government be so insensitive and humane to eliminate the efforts to educate their citizens about the leading environmental calls of cancer mortality? Eleven years ago when my -- when the oncologist told my husband, and he got lung cancer, it would take his life, we had no idea that we have been living with this invisible killer radon for 18 years because our society is so ignorant of the danger of this gas that cannot be seen, smelled or tasted. No one seems to care about those of us who have been robbed of our loved ones and our lives.

We have a government to protection for us, not just on the battlefields but in our indoor environment as well. The cause of lung cancer treatments amounts to 100s of 1,000s of dollars per patient.

And there is only a 15 percent to 17 percent five-year survival rate. In contrast, the typical home can be (at a) mitigation system installed $4,000 or $1,500 if they are aware of the danger.

State and federal staffing and program grants are essential for the government's moral, duty, legal obligation and of risk reduction to our American public.

I urge the members of Congress to ensure the continued existence of a fully funded radon program in EPA to protect our citizens against this leading environment cause of cancer mortality, this radioactive killer. They have the power and opportunity to save these lives 21,000 a year. You can make a difference.

The federal law, the Indoor Radon Abatement Act was passed in 1988, which it stated the government would protect the citizens from radon gas with state radon programs providing education and awareness. Please don't go back on your word, your actions, to support this critical live-saving program is vital. Thank you very much.

Andrea Drinkard: Thank you very much, Gloria. Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Jeff Arnold.

Jeff Arnold: Hi. I am…

(Off-Mic)

Jeff Arnold: … representation of a new organization. I came to this process today. That has been extremely enlightening in how the new administration is completely

curtailing in cunning out public comments by reducing this to a three-hour conference call on a Monday in which no working person would be able to attend reasonably without being an activist in the space or a representative of a major corporate interest. This is not only unfair. It should really be (outright)…

(Off-Mic)

Jeff Arnold: My concern is that the repeal of the Clean Air and Water Act will essentially have huge implications disproportionately affecting people based on cost and rates because those who have least ability to afford moving will be most impacted by environmental concerns nearby them.

Externalities are not well accounted for in the free market and there is no effective means of combating that without regulation in our current marketplace. Acknowledging that, in tandem with acknowledging the fact that there is a massive subsidization of the entire fuel industry when you account for tax write-offs for exploration and processing, we literally have put trillions of dollars of subsidization into these industries that have distorted the free market value of what they provide and have ignored the health costs that are rampant surrounding this work.

If we truly had equal terms, sustainable and low impact energy, we'd be way ahead and it already is in terms of job production. I am merely an individual with a background in economics contributing this information. I am horrified, absolutely horrified at the generate level of contribution you have seen from reps from industry who have seemingly no concern about the massive sweeping of deleterious effects that are about to be suffered nationwide should this repeal happen in the way it is about to happen. Thank you for your time.

Andrea Drinkard: Thank you very much, Jeff. Operator, would you open the next line, please?

Operator: Certainly. And as a reminder, if you would like to make a comment, please star-1 on your telephone keypad. Our next comment comes from the line of (Jim Spitz).

(Jim Spitz): Hello. I would like to question the calculus being used by the EPA here in this Executive Order in assessing costs and benefits particularly in regard to climate change and the rules most directly relevant here are the Clean Power Plan and methane abatement rule and the fuel efficiency standards.

We need to be absolutely clear that if scientists are anything close to correct than the regulatory burden of failure to bring in climate change under control will be far beyond anything in the experience of human civilization.

The burden of having an atmosphere that consists of 410 parts per million carbon dioxide, the number that is rapidly increasing will vastly exceed anything that any industry representative could possibly complain about.

I live in Gatlinburg, Tennessee where we were just burdened with a wildfire last November which was a result of the driest autumn in memory. That would not happen in the normal climate. That is a burden imposed on us by the EPA's failure to regulate greenhouse gases.

I think we must also call attention to the elephants in the room here that we have an EPA administrator who has publicly and with impunity contradicted the basic scientific understanding of climate change. This is unacceptable. The EPA cannot make policy based on fiction.

In the future, the American Southwest will be burdened by a permanent drought. Anyone living within three feet of the ocean will be burdened by a sea level rise. This can't be ignored by EPA. It must move ahead with the Clean Power Plan and the methane abatement rule and the fuel efficiency standards.

I ask EPA to please disregard the objections of industry that are absolutely inconsequential and insignificant by comparison. Thank you.

Andrea Drinkard: Thank you very much, (Jim). Operator, next line, please?

Operator: Our next comment comes from the line of Sarah Fields with Uranium Watch.

Sarah Fields: Hello. I am concerned that the current administration of EPA are more concerned about the burdens of regulations on profit-making industries rather than the health and social burdens on their citizens particularly those at risk.

I also need to respond to a comment about how nuclear power is an emissions-free industry, it certainly is not. The nuclear industry relies on fossil fuel at every stage of the nuclear fuel's chain from the point of exploration for uranium, uranium mining and milling, manufacturing of nuclear fuel, construction and operation of reactors and the handling and disposal of nuclear wastes. Of course, we still do not have a final solution to the disposition of high-level nuclear wastes, so the EPA doesn't have a basis for evaluating those impacts.

The nuclear industry also includes emission of radioactive and hazardous materials. The EPA is a regulatory agency. Regulatory agencies must have a document control system that ensures the permitting documents are made readily available to the public electronically and in a timely manner.

The Nuclear Regulatory Commission does that with their ADAMS electronic reading room, which is a good example of how public documents should be made available in a timely manner.

I am concerned about the lack of current health research related to radioactive emissions and impacts on community. I also would like the EPA to increase its oversight over state programs that implement the Clean Air Act.

The EPA should conduct timely regulatory reviews of state programs at least every two or three years and provide public input in those reviews. I shouldn't have to go to the EPA to get the EPA to tell the state of Utah that they -- what to do.

(Crosstalk)

Andrea Drinkard: Your line is still up.

(Off-Mic)

Sarah Fields: Does that signal that I am done?

Andrea Drinkard: You have about 15 seconds left.

Sarah Fields: Oh. OK. I'm very concerned too about the EPA Subpart W rulemaking for radon emissions from uranium mills. And the indifference and lack of concern for the public that live in the vicinity of uranium recovery facilities does not bode well for further decisions by the Office of Air and Radiation.

Andrea Drinkard: Thank you, Sarah. Your time is up. Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Sarita Hudson with Partners for a Healthier Community.

Sarita Hudson: Hi, this is Sarita Hudson. I am the Director of Programs and Development for Partners for a Healthier Community, the public health institute of Western Massachusetts. And I convene the Pioneer Valley Asthma Coalition.

In Springfield, Massachusetts, fully 1/5 of our students have asthma. It's even higher in Holyoke, Massachusetts where 30 percent of kids have asthma. Asthma has been directly linked to air pollution, and in particular, to clean -- to power, the particulate matter that comes from power plants and to traffic-based air pollution.

It is critical that we maintain regulations that as we look at regulations that we also look at what is the burden on health and the economic and social impact of health problems related to air quality, whether it's radon, whether it is -- it is from power plants or -- and in particular, we would also consider the air -- indoor air impacts that come from having lead-based paint and other regulations that deal with hazardous substances, radon, lead, asbestos.

It's really critical that in looking at any of these in considering what is burdensome that they -- that there is also a consideration of what are the health impacts on children and what that means in terms of their education

and their productivity as adults and their ability to work and have fulfilled lives.

So, as we look at where the EPA regulations and in particular, those that will drive climate change which again will have serious health impacts and is already starting to show health impacts that we consider that all considerations around those -- any regulations that would have a health impact that that is considered fully as well as any burdens that are on industry -- industries or companies to implement those regulations.

In particular, we would also look at the focus on water quality as we found in Flint, Michigan that the need for regulation of water -- lead and water is critical. So, if anything, there should be even more regulations put into place to avoid the situation like Flint. Thank you very much for this opportunity, and we will be submitting written testimony.

Andrea Drinkard: Thank you very much, Sarita. Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Joseph Pendola with National Steering.

Tony Pendola: Hi, my name is Tony Pendola, I'm the Small Business Ombudsman for the state of North Carolina. But today, I'm here in my role as the Chair of the National Steering Committee for Small Business Environmental Assistance Programs or SBEAPs.

The Clean Air Act requires that each state and territory have someone that can provide free technical assistance and advocacy for small businesses. We work with OAQPS and other EPA groups. We greatly appreciate this opportunity and we'll follow up with written comments.

We have been providing comments to EPA for many years and we'll repeat a few today that has not gained any traction. I would be remised if I didn't mention our strong desire for greater interaction with the Office of Air Quality

Planning and Standards as we have significant state-specific expertise and regulatory reform.

We would like to see EPA rescind the "once in, always in" guidance policy since it discourages emission reductions and assist states with large biogenic sources of VOCs in efficiently determining at the summertime gasoline RVP standard can be rescinded as it has been in North Carolina, Florida, Alabama and Pennsylvania. And this could result in saving billions of dollars for drivers and reducing refinery emissions.

One of the rules I'd like to talk about today is the auto body NESHAP or 6H. After the rule became effective, all of the major paint manufacturers reformulated their traditional automotive paints to all but eliminate those containing the heavy metals targeted by the rule.

Unfortunately, this is perhaps the only rule of its kind that assumes an entire sector consisting of 10s of 1,000s of auto body shops uses products containing these heavy metals. If the regulation were modified to treat auto body shops like all other facilities subject to this regulation and then the shops would no longer be automatically covered. In fact, hardly any of them use those materials any more. They would only be covered if they use them that contain the target heavy metals as laid out in the applicability section.

Another rule we'd like to discuss is the NSPS for petroleum dry cleaners. Comments were previously submitted and noted how this rule should not apply to newer dry to dry technologies. An applicability determination was issued on November 17th of 2015 by Region 4 stating that for the first time that newer dry to dry machines are not covered by the definition of petroleum dry cleaner.

Very few of the 10s of 1,000s of owners of these machines are aware of this dramatic change in interpretation. This significant of a change needs to be codified in the regulation itself and can be done by simply changing a definition. Thank you for the opportunity.

Andrea Drinkard: Thank you, Tony. Operator, would you open the next line, please.

Operator: Our next comment comes from the line of Angela Tin with American Lung Association. Angela, your line is open.

Angela Tin: Hello, my name is Angela Tin, and I am Vice President of the -- of Environmental Health for the American Lung Association of the Upper Midwest. Thank you for allowing us to speak today. I will also be providing written comments.

Radon is a colorless, odorless and tasteless gas that comes from the breakdown of naturally occurring uranium in the soil. The location of greatest exposure to radon is in the home. Radon can enter homes through cracks and other pathways in the foundation.

Any home can have radon regardless of new or old construction. Radon is a known human carcinogen that can cause lung cancer, is a leading cause of lung cancer among nonsmokers and is responsible for 21,000 lung cancer deaths each year. About 3,000 of these deaths occur from people that have never smoked.

The U.S. Surgeon General says that breathing radon over prolonged periods can prevent -- present a significant health risk to families all over the country. EPA estimates that 13 percent of lung cancer deaths are radon-related and that one in every 15 homes have a high level of radon above the recommended action levels.

We urge EPA to continue to maintain the existing radon program. Radon is a serious problem with a simple solution. The American Lung Association and all of our radon partners are working together to remove radon in our homes, workplaces and community with your support. Thank you for listening to me and your time.

Andrea Drinkard: Thank you, Angela. Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Nathaniel Burden with Fidelity Inspections.

Nathaniel Burden: Yes. Hi. This is Nathaniel Burden from Fidelity Inspection and Consulting Services, also representing the Pennsylvania Board of the American radon scientists and technologists, and following up on the radon issue since radon is a classic carcinogen that caused us 21,000 lung cancer deaths a year.

And as said before that it's the primary cause of lung cancer for nonsmokers, we strongly recommend that the Radon Action Program and the State Indoor Radon Grant program be preserved for risk communication to low income and minority communities.

Also, with the effort of reducing 21,000 lung cancer deaths to by 50 percent would cause a tremendous savings to the overall medical community and impact to the medical community on preventing lung cancer deaths.

So, my final statement is that we need to preserve the Radon Action Program and the SIRG grant in an effort to make sure that especially low income and minority communities are provided the proper information which they have not been. Thank you.

Andrea Drinkard: Thank you, Nathaniel. Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Gail Payne with Sierra Club.

Gail Payne: Hi, my name is Gail Payne and I'm the Nuclear Issues Chair of Sierra Club Long Island group. I am an unpaid volunteer, unlike most of the callers who want regulations weakened.

A recent caller that nuclear energy provides emission-free energy, this is untrue. Nuclear reactors release many types of radioactive emissions through day-to-day operations. If the caller was referring to carbon emissions, construction, maintenance, decommissioning and the processing of fuel and waste all have carbon emissions that exceed any renewable source.

Now, for my comment, the EPA was created for the purpose of protecting human health and the environment by writing and enforcing regulations based

on laws passed by Congress. I'd like to comment on a subject of repealing or modifying radiation standards to make them less burdensome.

I assume this means less burdensome to business, but do you know what is really burdensome to millions of Americans, cancer, asthma and birth defects. I am all for modifying the radiation standards to make them less of a health burden to you as citizens.

Permitted levels for radiation exposure were raised a few years ago, probably in response to the massive amount of radiation released by Fukushima. The incidence of cancer continues to rise worldwide in tandem with rising levels of manmade background radiation.

Background radiation has risen 600 percent since the start of the atomic age. The U.S. ranks sixth highest out of 50 countries in cancer incidents. Our allowable limits of radiation have been based on an arbitrary risk to an adult male.

However, women and children are much more sensitive than men to radiation. This means women like me and children like mine will be unduly burdened. There is no safe dose of radiation. All the reports of the National Academy of Science affirmed the no safe dose findings.

EPA, please, do not relax standards to either radiation or air pollution, when they should, in fact, be improved. That's it, thank you.

Andrea Drinkard: Thank you very much, Gail. Operator, next line, please?

Operator: Our next comment comes from the line of (Carrie Hugo).

(Carrie Hugo): Hello. Thank you for this opportunity to comment on implementation of Executive Order 13777. Firstly, I would like to thank the civil servants working for the EPA to help protect public health and our environment. Your work is often unrecognized, and sadly, it has become a habit for the hard work of civil servants to be a target for frustrations of those who would rather not

be burdened with the regulatory requirements that safeguard our air, water and food.

I have reviewed our nation's air status report for 2015 on the EPA website. This report indicates that despite a growing population, many of the harmful pollutants that affect our air, our climate, our health and our ecosystems are decreasing in much of the United States.

And while there's always room for improvement, we (are comforting) to see that the current regulations are clearly having a positive impact on our air quality and decreasing our exposure to pollutants.

Air pollutants in some categories have decreased by as much as 99 percent. It is very difficult to argue with the effectiveness of these results. Thus, I would question the reasoning behind reducing or eliminating these protections.

Finding efficiencies within an organization makes sense under any business scenario by reducing resources and changing regulations to the point that the EPA can no longer implement its own mission makes no sense.

The mission of the EPA is not to stimulate the economy or to reduce the regulatory burden on industry or special interest. The mission of the EPA is, "to protect human health and the environment."

I urge the EPA to temper the desire to stimulate the economy by relaxing the regulations that have helped the agency achieve the positive results that can be measured so far and the future results that will further protect their air quality even as our population grows.

Currently, renewable energy jobs outnumbered those in the fossil fuel industry and the trend for renewable energy sector is increasing while jobs provided by the fossil fuel industry are decreasing, which is the trajectory that needs to continue in order to reduce the impacts of climate change and protect public health.

The Clean Air Act, the Clean Power Plan and other regulations that impact air quality actually stimulate the economy and to grow in a way that will bring our country closer to sustainable and energy independence, sustainability and better health.

A dirty economy that causes us to move backwards and air quality and increases the presence of pollutants in our environment cannot help those who are suffering from the health effects caused by pollutants including asthma, various cancers and respiratory illness.

Any reduction or elimination in regulations, a reduction in staff to implement and enforce them that is based on cost savings down to implementation of Executive Order 13777 should include an in-depth economic analysis of how those potential savings to industry may actually result in higher cost to the consumer through higher healthcare cost, lost of quality of quality of life and cost associated with mitigating the negative impact of decreased air quality and increased toxic pollutants.

Any reduction or appeal of regulations that can…

Andrea Drinkard: Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Edward Smith with General Aviation. OK,
Edward, your line is open. You may be on mute. We're still not hearing you, Edward. Your line is open.

Edward Smith: Can you hear me? Can you hear me?

Andrea Drinkard: Yes, yes , we can hear you.

Edward Smith: All right. On March 6th of this year, the Council of the International Civil Aviation Organization, ICAO, adopted a new carbon dioxide emission standard for aircraft, the first of such design certification standard among world industry sectors, approved by the 36 emission councils codifies recommendations made by a committee of experts in February 2016.

The standard applies to new aircraft type designs as of 2020 into designs already in production as of 2023. Aircraft that are already in production must meet the standard by 2028 or be sufficiently modified.

This landmark standard was the product of six years of long and arduous work and reflects the cooperation and collaboration among the aviation industry including the general aviation industry, national regulatory authorities and other stakeholders including environmental groups.

The new standard is the product of input from our manufacturers and has our industry support. The new CO2 standard is one important component of the global aviation manufacturing industry's commitment to do its part to improve its efficiency and mitigate its effect on climate change.

The next step in the process is for national authorities, in the case of the U.S., this means that EPA in cooperation with the FAA to issue regulations implementing the new global standard. The General Aviation Manufacturers Association representing the U.S. and global aviation manufacturing industry urges the U.S. government in the strongest possible terms to develop the appropriate implementing regulations in a timely manner to ensure that U.S. manufacturers are not disadvantaged in the global marketplace.

Failure to implement the new CO2 standard for U.S. manufacturers would harm their ability to get aircraft certified for operation and sale into markets around the world. This has the potential to seriously harm the competitiveness of one of our nation's most competitive industries and one that provides many 1,000s of well-paying high-tech jobs.

The general aviation industry by itself supports $219 billion of total economic output and 1.1 million jobs in the United States. Thank you very much.

Andrea Drinkard: Thank you, Edward. Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Lauren Pagel of Earthworks,

Lauren Pagel: Yes, hello. My name is Lauren Pagel. I'm the Policy Director of Earthworks, an organization that protects communities and the environments and the adverse impacts of mineral and energy development.

I'd like to comment on the New Source Performance Standards for methane emissions from the oil and gas industry and urge the EPA to not only keep these important standards in place but rigorously enforce them. These safeguards are more important to protect public -- are important to protect public health and the climate from air pollution that impacts millions of people across the country.

Over 12 million who live within a half mile with an active oil and gas facility and bear the brunt of the health impacting this industry including some 150,000 asthma attacks caused by oil and gas air pollution alone.

In addition to the immediate health impacts of volatile organic compounds like benzene, methane is especially quoted climate pollutant, warming our planet 80 times faster than carbon dioxide over a 20-year time period.

One quarter of the climate disruption we are experiencing today comes from methane pollution. The EPA should be about protecting public health in the environment, not catering to energy companies' desire to pollute more. No clean air regulation should be rescinded or weakened at the behalf of the industry creating the pollution. Thank you.

Andrea Drinkard: Thank you very much, Lauren. Operator, next line, please?

Operator: Our next comment comes from the line of Heidi McAuliffe, American Coatings Association.

Heidi McAuliffe: Thank you. My name is Heidi McAuliffe. I'm with the American Coatings Association. And I want to say thank you, first of all, to EPA for holding these listening sessions. I think it's very good idea to get these kind of comments from a broad spectrum of your audience. We will also submit comments in writing as well.

I'd really like to just address one issue today, and that is the "once in, always in" policy under the NESHAP for source categories. This actually is not even a regulation, it is a policy memorandum that was issued on May 16, 1995 by EPA. It's called the Potential to Emit for MACT Standards -- Guidance on. Timing Issues from John Seitz, Director of the Office of Air Quality Planning and Standards, OAQPS. And it was issued to the regional division directors.

Pretty much, everybody refers to this policy as the "once in, always in" policy. And I know that it's been referenced at least one or twice already by other commenters. Anyway, the -- under the MACT standards, a major source is defined as a source that has the potential to emit hazardous air pollutants of up to 10 tons per year of any single HAP or 25 tons per year of any combination of HAP.

Sources below this threshold are considered area sources, but under the "once in, always in" policy, a major source may become an area source by limiting its potential to emit these HAPs to below the major source thresholds. But there was a compliance deadline issued under the maximum available control technology standards, which is also called the NESHAP.

If you neglect it or if you fail to achieve that area source standard by the very first compliance deadline then you remain subject to the MACT even if you subsequently reduce your HAPs admissions to below major source levels at any other point in time.

So, as I said, if you don't get your emissions below that particular threshold by the deadline, you're subject to the MACT no matter what efforts you take in the future to reduce your emissions.

The coatings industry has substantially reduced all use of HAPs significantly and we have many, many companies that have or way under this threshold that are not able to get underneath that requirement in the "once in, always in" policy.

We would really appreciate if EPA would reconsider this policy and withdraw or rescind it. It really does not encourage manufacturers to reduce emissions because of this policy. So, we will be submitting comments on this as well and look forward to doing so. Thank you.

Andrea Drinkard: Thank you very much, Heidi. Operator, next line, please?

Operator: Our next comment comes from the line of Melinda Ronca-Battista, Native American Tribe.

Melinda Ronca-Battista: Hi. Thanks for hosting this session. It's really great that the EPA allows public comments on significant changes that may be happening.

I have just a quick comment in a way that could reduce burden and actually increase environmental measurements which is to reduce the burden and requirement for quality assurance project plans for projects that don't even involve gathering data.

This is a great burden for the many small agencies such as tribal agencies. In the past, EPA has required quality assurance project plans for using EPA's own data to draw a conclusion as well as things that obviously don't need a QAP such as literature searches.

So, that's my only comment. I'm hoping to be practical and productive and thank you, EPA, it's the best federal agency we've worked with many. And we appreciate this time to comment, reduce the burden of craps. Thank you.

Andrea Drinkard: Thank you, Melinda. Operator, next line, please?

Operator: Our next comment comes from the line of Christian Peña with Appion Inc.

Christian Peña: Yes, thank you. I'm Christian Peña, Executive Manager of Appion Inc. in Denver, Colorado. Our company manufactures tools and equipment used to recover and capture refrigerants specifically substances known to harm the ozone and equipment and contribute to global climate change.

I'm speaking on my own behalf on the basis of my direct experience with this industry working successfully under EPA regulations for decades. I've been closely involved with the work required to capture, track and manage these substances, procedures that are sometimes associated with added time and cost.

While it would be easier to irresponsibly vent these substances, the impact of such carelessness has been well documented. The smoking gun of manmade substances destroying stratospheric ozone cannot be ignored.

I have heard and read other commenters essentially asking the EPA to rollback regulations because of the concern that it's hard or expensive to protect the environment. They have also been requests to the level of the playing field by finding the lowest common denominator in regulation.

Electrical generation oil and gas industry representatives even here today have acknowledged how incredibly successful they have been even with the continued regulatory oversight of the EPA and therefore show that EPA's actions have not been unnecessary burdens.

If EPA is going to seriously pursue the modification of regulation then it is critically important that decades of work on protecting the environment not be ignored. For each area of regulation that the EPA has enacted on behalf of the American people and our health by way of clean water and clean air, it is necessarily that extensive review occur that meets or exceeds the amount of review that occurred when initially enacting each and every rule.

Public health must remain the first priority above any industry profits. For industries that cannot succeed without harming the environment, the cost to allow them to proceed is simply too high.

Clean water and clean air are the legacy that we must all work towards providing our future generations. While it is certainly possible and reasonable to review and update regulations, it must be done responsibly. Your responsibility is to protect our air and water.

For every rule withdrawn and regulation rolled back without significant irresponsible review to ensure that public health remains a priority, EPA and the current administration will have failed the American people and the world for generations to come. Thank you.

Andrea Drinkard: Thank you, Christian. Operator, next line, please?

Operator: Our next comment comes from the line of (Riley Meyer).

(Riley Meyer): Hello. Can you, guys, hear me?

Andrea Drinkard: Yes, we can hear you.

(Riley Meyer): Wonderful. I'm here to speak about (Vital Point) then. Although it may not be sexy in any particular way, it's something that goes and talked about in many of these issues.

(Vital Point) on the low ANGA estimate of 50 percent of our air. As water temperature rises, they are dying, and with that goes more than 50 percent of the entire world air as well -- as well as the principal food supply of most fish and other -- and the food supply of most of our planets.

We cannot afford to have a lacking EPA, whether you are corporate or if you are -- or if you are a private citizen, it goes about saying that we need (Vital Point) and we need to have the information provided by each corporation to provide EPA regulatory information, otherwise, the EPA cannot react to the pollution of each corporation.

I find over and over again throughout this teleconference that it's much tough that the corporate -- some corporate representation, the economic burdens on them would resolve only in the economic burdens of the American people. That's an incredible over simplification of the issue and it is in the corporation's self interest to persist this (inaudible) that their burdens are synonymous with the American people.

Please look to places like Dish, Texas, promise with jobs (including) industries. They instead receive chemical infused water that cost virtually every citizen millions of dollars in medical bills and plummeting costs of their housing which is the principal form of capital.

None of these are provided in the corporate estimates of projection submitted to these forums. The American people are not considered in these projections because it's not in the corporates' best interest to include them.

This isn't a new story. Dish has existed in many other places from Flint, Michigan to Hinkley California and the ever-burning coal mine of Centralia, Pennsylvania. They're not here necessarily to make jobs. They're here to get as much money as they can in the short term. And I can't fault them for that, but it's up to the EPA to see what they're doing, understand what they're doing and working nimbly to fight against them.

Thank you very much for hearing my words. I hope that you can find something that will -- I hope that you will not repeal the plea, EPA, it is so important. And we've seen 70 percent -- we've seen 69 percent better quality air since the 1970s of the Clean Air Act. It clearly does something and it's something that we valuably need. Thank you.

Andrea Drinkard: Thank you, operator -- thank you, (Riley). Operator, next line, please?

Operator: Certainly. As a reminder, to ask -- to make a comment, please press star-1 on your telephone keypad. Our next comment comes from the line of Ashley Soltysiak with HEAL Utah.

Ashley Soltysiak: Hi, this is Ashley with HEAL Utah. I'm HEAL Policy Director. HEAL Utah is a nonprofit with campaigns focused on clean air, clean energy, nuclear wastes and power policies.

I just like to make a statement today on behalf of my organization and our 15,000 members across the state of Utah. We're based in Salt Lake City, one of the areas in the country with the worse air quality during both the winter for particulate matter -- P.M. 2.5 and ozone in the summer.

This causes some of the highest incidences of asthma, cancer, stroke and exacerbated cardiovascular and respiratory problems and increases mortality rates in our area. It hurts our environment and public health and our capacity for economic growth in the future.

Frankly, the vast majority of improvements to air quality that we've seen in our state have been because of federal air quality standards like tier 2 fuels for vehicles. We need a strong federal oversight, not repeal and replace policy that's focused on short-term business gains at the expense of our families and our environment.

Therefore, we urge the EPA to strengthen the National Ambient Air Quality Standards under the Clean Air Act rather than weaken these critical health standards. In particular, we urge the agency to maintain the current ozone standards and make them even more robust rather than weaken them.

We also urge the continued reinforcement of the Regional Haze Rules which are critical to maintaining the air quality in our five beautiful national parks that are bordered by coal-fired power plants and extensive extractive industries.

Frankly, those of us here in Salt Lake City cannot breathe during our wintertime inversions and our lungs are being burned by excess ozone pollution in the summer. We also have a strong nuclear legacy in the state of Utah and urge the agency to maintain radioactive safeguards.

Ultimately, we believe that this means improving and enforcing EPA's air quality standards which are imperative to maintaining our industries, our diversified economy, improving our public health and working towards healthy and sustainable futures for generations to come. Thank you.

Andrea Drinkard: Thank you, Ashley. Operator, next line, please?

Operator: Our next comment comes from the line of Barry Andrews with Air Quality Services.

Barry Andrews: Thank you. My name is Barry Andrews. I am an air quality consultant with more than 35 years experience in the profession. Ten associates were working for regulatory agencies with multitude of duties including rulemaking activities.

Some of those rulemaking activities include working in tandem with EPA to develop regulations for air emission sources which we knew at the time were inadequately controlled. An example of this was the development of New Source Performance Standards for municipal waste combustors.

Following my experience working with the regulator, I have spent the last 25 years providing consulting to multiple industries including oil and gas companies whose operations are at the upstream, midstream and downstream levels.

During this time, I've seen EPA developed programs that have benefitted both industry and the environment and represent a good example of the things that EPA should pursue. An example of this is the Natural Gas STAR Program.

On the other hand, in recent years, I have seen three examples which I would clearly identify as being overly burdensome to industry. An example of this is the Greenhouse Gas Reporting Program per 40 CFR Part 98 Subpart W.

For the last six years, greenhouse gasses emissions data has been submitted for numerous activities. It is clear from looking at the data year after year that there are just a few activities that represent the vast majority of total greenhouse gas emissions.

Yet, year after year, the industry is required to report for the same activities that were part of the initial rulemaking activity. Following this procedure results much time and effort to account for greenhouse gas emissions that account for a very small percentage of total.

I would encourage EPA to return to their efforts back to what I would describe as a common sense to regulatory activities and seek to identify and focus on

what measures would result in massive environment benefit and at the same time, not overburden industry. Thank you for the opportunity to share my comments.

Andrea Drinkard: Thank you, Barry. Operator, next line, please?

Operator: Our next comment comes from the line of Gary Garrahan with STIHL Incorporated

Gary Garrahan: Thank you. Hello and thank you. STIHL Incorporated is a manufacturer of handheld outdoor power equipments such as chainsaws and leaf blowers. We ask EPA to consider reducing the regulatory burden in situations where one set of regulatory requirements exists for the air emissions resulting from the operation of products while another set of regulations apply to air emissions resulting from the manufacturers; testing of these products.

Specifically, as a manufacturer of gasoline-powered outdoor equipment, we are required to meet the EPA requirements for small non-road engines while at the same time, as a facility, we're required to have a federal air permit due to our potential to emit resulting from the testing of these engines.

Now, bear in mind, we run each engine in our facility for at most a few minutes in order to ensure that it meets emissions requirements while the end-user, the customer, will run that same engine for years to come.

Meeting the small non-road engine requirements ensures that the engines will have low emissions, so maintaining a facility air permit is really unnecessary for both the regulator and the regulated community.

The small non-road engine regulations are focused on reducing emissions, the facility air permit is not. It is really a little more than a database. If EPA can make allowance for situations where as long as manufacturers meet the emission requirements for their products then they would have a reduced burden with regard to air permitting requirements for the facilities in which they produce these products. Thank you.

Andrea Drinkard: Thank you, Gary. Operator, next line, please?

Operator: Our next comment comes from the line of Oscar Paulson with Kennecott Uranium

Oscar Paulson: Thank you, ma'am. My name is Oscar Paulson. I'm a Facility Supervisor at Kennecott Uranium Company, Sweetwater Uranium Project, which is a licenses conventional uranium recovery facility located in Sweetwater Country, Wyoming.

I would like to propose the following two items for repeal under this Executive Order which are as follows. The first is the proposed rule, Health and Environmental Protection Standards for Uranium and Thorium Mill Tailings, Federal Register Volume 82 Number 12, Thursday, January 19, 2017 on the proposed rules.

It is the belief of industry that this proposed rule directed primarily against in-situ uranium recovery operations is not justified by the risks post by these operations specifically because these operations conduct their activities with an exempted portions of…

(Off-Mic)

Oscar Paulson: The second item that I would like to propose for repeal would be the final rule Revisions to National Emission Standards for Radon Emissions from Operating Mill Tailings. This is listed under Federal Register Volume 82 Number 10, Tuesday, January 17, 2017 under rules and regulations.

It is the belief of industry that this final rule is again, not justified by the very minimal risks post by the types of operations it regulates or attempts to regulate specifically uranium mill tailings impoundments, evaporation ponds at licensed uranium recovery facilities and uranium heap leach pads because this type of facilities are as a general rule located in very, very remote areas, and as such, don't post great risks or hazards to general public.

We also intend to submit written comments as well by the deadline. And thank you for allowing me this opportunity to comment.

Andrea Drinkard: Thank you very much, Oscar. Operator, next line, please?

Operator: Our next comment comes from the line of Paul Balserak with American Iron and Steel.

Paul Balserak: Hi, my name is Paul Balserak and I work for the American Iron and Steel Institute. AISI serves as the voice of the North American steelmakers, are 19-member companies and 125 associate members, represent real men and women across America who work in the job of steel production and manufacturing.

The steel industry has been hit by significant cost of job losses over the past years. We care deeply about our environment, and as an industry, have worked very hard to significant reduce our emissions and energy use over the past decades.

We also care deeply though about the work of men and women in the steel industry who have families they most care for. Their lives are generally harmed by the routine and significant cost and delays in projects at their plans from the federal air permitting regulations.

We are very encouraged by this opportunity for evaluation of current regulations. We want to maintain a clean environment around our plants but often find the way air rules are implemented results in real challenges to U.S. production of steel and the competitive world market.

We hope in particular that there will be a focus on streamlining the new source review programs such as allowing routine maintenance at plants to be completed more quickly and easily without unnecessary delays.

We also hope that EPA could make improved modeling tools a higher priority. While we appreciate the recent Appendix W Air Dispersion Final Rule, we would hope that the rule could be changed in -- to enhance particular

areas would receive widespread comment during EPA;s work on this recent final rule.

When the timing of air permit decisions by the federal government, not the actual air standards themselves at the facility but the timing of getting a permanent modification itself to process becomes a key deciding factor in major financial decisions on whether to expand the given plant.

There's something wrong with the way the air rules are being implemented. We appreciate this opportunity and look forward to work closely with the agency in public news and common process as we continue to enhance our environment and the way the air permit rules work. Thank you very much.

Andrea Drinkard: Thank you, Paul. Operator, next line, please?

Operator: Our next comment comes from the line of Nancy Kirner wit Health Physics Society

Nancy Kirner: Hello. My name is Nancy Kirner and I'm past President of the Health Physics Society and Chair of its Scientific and Public Issues Committee. HPS is the professional organization of specialists and radiation safety and we thank you for this opportunity to express our concerns.

First, the HPS appreciates the efforts of the EPA in protecting public health and the environment. We've had an exemplary working relationship with EPA and we hope that we'll continue well into the future.

Today, our primary regulatory concern is EPA's apparent reliance on the linear non-threshold hypothesis, LNT, especially at low doses and low-dose rates without consideration for the uncertainty of estimated health effects at low doses.

This reliance tends to foment the public's irrational fear of all types of radiation. This adherence to LNT goes against the International Commission on Radiation Protections Report Number 103, which states in part, corrected effective dose is not intended as a tool for epidemiological risk assessment

and it's inappropriate to use it in risk projections. In particular, the calculation of the number of cancer deaths based on collective effective doses from trivial individual doses should be avoided.

The HPS has a similar position statement called radiation risk perspective available at www.hps.org. it recommends against estimating health risks when exposes to ionizing radiation are near or less than natural background levels especially when doses are less than 100 millisievert from all no-background sources.

The following EPA documents could be improved to better address these uncertainties, the EPA assessment of risks from radon in homes especially.

Federal Guidance Reports Number 11, 12 and 13, EPA radiogenic cancer risk models and projection for the U.S. population also known as the Blue Book and…

(Off-Mic)

Nancy Kirner: …radionuclide tables, radionuclide, carcinogenicity slope factors.

And, of course, all of this gets embodied into 10 CFR 190 and 40 -- excuse me, that was 40 CFR 190 and 40 CFR 192. These could be reduced with additional epidemiological research to better quantify potential effects of low level radiation exposures.

We look forward to working with our colleagues at EPA to improve the existing regulations and seek additional epidemiological research on low levels of radiation. We'll also be submitting written comments. Thank you very much for the opportunity to speak.

Andrea Drinkard: Thank you, Nancy. Operator, next line, please?

Operator: Our next comment comes from the line of Ulla Reeves with National Parks Conservation Association.

Ulla Reeves; Hi, good afternoon, my name is Ulla Reeves and I'm with the National Parks Conservation Association speaking on behalf of our 1.2 million members and supporters who include a wide range and diverse group of baby boomers and millennials, liberals and conservatives, history (busts) and outdoor enthusiasts. They all share commitment to preserve America's past and protect our future, a concept that is at the heart of America's national parks.

We advocate for the health of national park ecosystems and the billions of people who cherish them and visit every year. In fact, just last year, our national parks generated nearly $35 billion for the U.S. economy, supporting 320,000 jobs across the country.

We are deeply concerned about the EPA's process and motivation for repealing, replacing or modifying regulations that we believe are critical to the future of our treasured national parks. EPA plays a fundamental role in safeguarding our iconic public lands and their air, water, wildlife and the people who visit them through the environmental regulations that exist today.

Because most resource threats exist beyond park boundaries, they are ultimately under EPA's regulatory jurisdiction, it is EPA's duty to ensure that state implementation and enforcement of the environmental regulations comfort with bedrock laws like the Clean Air Act and Americans depend on EPA to work with federal land managers including the national park service industries, states and the public to safeguard our pristine wild places and mitigate existing or potential threats.

We often press for more stringent safeguards because their quality problems are very much still in existence but we recognize that EPA has typically served its park protection duties in earnest.

The Office of Air and Radiation has delivered enormous benefits to the public in upholding the Clean Air Act visibility protection mandate as well as its good neighbor and acid rain programs.

Over the last 15 years, the advancements of these and other critical clean air policies have restored an average of 20 miles of visibility in the East and places like Shenandoah National Park and Okefenokee National Wildlife Refuge. And in the West, these programs have returned 30 miles on average of clear views to places such as Arches National Park and John Muir Wilderness.

These same policies make it safer for children to breathe and support longer park stays thus even further bolstering local economies.

We respectfully request that instead of pursuing repeal or weakening of regulations named in the executive orders, the EPA ought to continue to implement and enforce the sound regulations already on the books.

EPA ought to be asking how to better and more efficiently carry out its mission of protecting public health in the environment, not how to retreat from it by minimizing safeguards. We ask that EPA amend its current process by holding public hearings across the country to fully consider citizen and stakeholder input on regulatory reform and we urge EPA to make this process more thorough and balanced. Thank you for your time and consideration.

Andrea Drinkard: Thanks, Ulla. Operator, next line, please?

Operator: Our next comment comes from the line of Richard Wells Fargo with Offshore Marine Services.

Richard Wells: Good afternoon, everyone. I wish to address an unintended negative impact on U.S. shipyards by the recently implemented North American Emissions Control Area or ECA. The International Maritime Organization or IMO through the International

International Maritime Organization or IMO through the International MARPOL Convention Annex VI designated the coastal waters of the United States as an ECA. Under MARPOL Annex VI and the related U.S. EPA rules and the act to prevent pollution from shifts, no vessel built on or after January

1, 2016 with an IMO tier 2 engine can operate that engine within the North American ECA.

A U.S. shipyard building a vessel with an IMO tier 2 engine for use outside the North American ECA is prevented from testing and delivering the vessel without violating the MARPOL and EPA rules.

Also, any ship built outside the United States in 2016 or later with an IMO tier 2 engine is prohibited from entering the ECA to transit to any U.S. shipyard for repairs or dry docking. Further, a dual fuel ship both LNG and diesel fuel that was specifically built to exceed the IMO tier 3 standards will during a voyage to s shipyard for maintenance and repair of the ship or repair of the dual fuel engine is temporarily prohibited from using or carrying gas fuel and therefore would not comply with the IMO and EPA ECA requirements.

So, we urge the EPA to modify the act to prevent pollution from ships to match recent changes to IMO Annex VI which were proposed by the U.S. delegation to the IMO to address this situation.

This exemption would allow a ship with tier 2 engines constructed after the effective date of our ECA to operate in our ECA when related to original construction, conversion, maintenance and repair of the ship or maintenance or repair of a dual fuel engine while it is prohibited from using or carrying gas fuel due to repair facility safety requirements.

To minimize potential adverse environmental impacts of this exemption, the exemption could be subject to some additional conditions such as the exemption is temporary only long enough to allow the ship to proceed to and from the shipyard.

The engines onboard must meet IMO tier 2 NOx limits, the ship may not load or unload cargo while operating in the ECA and the ship sails directly to and from the shipyard, or in the case of a dual fuel vessel, directly to the nearest gas fuel bunkering facility located in the ECA.

Andrea Drinkard: Thank you, Richard. Your time is up.

Richard Wells: Thank you for this consideration of this -- a fix for this unintended impact to the U.S. shipyard industry.

Andrea Drinkard: Thank you, Richard. Operator, next line?

Operator: OK. Our next comment comes from the line of John Young. John, your line is open. We're not hearing you. John Young, your line is open.

Andrea Drinkard: Thanks, operator. I think we'll go to the -- to the next caller.

Operator: Our next question comes from the line -- our next comment, sorry, comes from the line of Terri McCartney with, Hopland Band of Pomo Indians.

Terri McCartney: Hello? Hello?

Andrea Drinkard: Yes, we can -- yes, we can hear you?

Terri McCartney: OK. Hi, I'm Terri McCartney with the Hopland Band of Pomo Indians in Northern California. And I'd like to remind everybody that air move, it is not restricted within boundary -- state boundary, travel boundary, reservations.

And it's critical to have a strong EPA with oversight of the air quality because having states take on jurisdiction and of regulations can have unintended consequences of the air quality throughout the region.

This is very important for EPA to consider when looking into repealing regulations that can impact tribes to try to -- this report -- this reporting an amount of asthma and respiratory conditions caused by poor air quality which is -- also has been impacted by inferior workmanship in housing with high levels of formaldehyde and (black mole) and other building materials.

So, we respectfully request that EPA consider all of the options when looking into changing regulations that could impact the (disadvantaged) communities. Thank you.

Andrea Drinkard: Thank you, Terri. Operator, next line, please?

Operator: Our next comment comes from the line of (Delena Triono) with Citizens.

(Delena Triono): Hi. Can you hear me?

Andrea Drinkard: Yes, we can hear you.

(Delena Triono): OK, great. My name is (Delena Triono). I'm a citizen of the United States and I'm not affiliated with any organization. I'm calling to strongly oppose dismantling any regulations provided and enforced in the Clean Air Act by the EPA.

These rules which have -- which were stated here are even decades ago already…

(Off-Mic)

(Delena Triono): …protect citizens and the environment. But they are all we have. However, it would be enormously detrimental to dismantle the laws that are in place.

I live in New York City and in New Jersey most of my life, and even with the existing rules, it is not uncommon to get air quality alerts, warning people to limit their time outdoors.

While living in New Jersey, we even have warnings from the city alerting us not to open our windows as there were airborne toxins being released into the air due to unearthing of toxic wastes nearby. This was -- it was so bad that our children in our local schools could not go outside and play during recess. We have -- they have to be kept indoors the whole day.

For weeks, the entire household, our entire household suffered from constant and severe headaches, vertigos, dizziness and general ill-feelings that lasted for months. We got to the point where our house has to be inspected for carbon monoxide poisoning and gas leakage.

Fortunately, everything in our home are safe, but it proves that the suffering was from the industrial activity that was going on in our city which caused

them to unearth those toxic wastes. We had to be moved out of the -- out of the city and into the countryside just so that our family could breathe without feeling ill.

While these are just my personal experience, they are not isolated incidents. In fact, there's a multitude of other and intimately more outrageous practices which while they are legal have devastating impact on the people and -- on the people that live in those areas.

The core access pipeline, the water practice in Flint, Michigan and the Exxon gas well exposure in Pennsylvania which killed one person and then the town people were later rewarded with pizza gift cards for their trouble.

These are all examples of widespread regulations that are while are protecting are just not doing enough to really do what the institution is supposed to do. All these -- all these actions were legal under current regulations, but these actions negatively impacted 1,000s of people in different areas of the country.

And in my personal experience, it made everyone in our city including all of the children in our school sick for weeks and months. Many of the people in the energy companies looking to rules and regulations for the sake of profits nor any of their family members will ever, ever have to (inaudible) through the negative impacts of the damage they are causing. They are biased by process.

Andrea Drinkard: Thank you, (Delena). Your time is up.

(Delena Triono): And this is what they are in favor of…

(Off-Mic)

(Delena Triono): Hello?

Andrea Drinkard: Yes, your time is up. Operator, would you, please, open the next one?

(Delena Triono): OK, sorry.

Operator: Our next comment comes from the line of Andy Bessler with National Tribal Air Association.

Andy Bessler: Thank you. Hello. My name is Andy Bessler, Project Director for the National Tribal Air Association. NTAA's mission is to advance air quality management policies and programs consistent with the needs, interests and unique legal status of American Indian tribes and Alaska natives.

NTAA has 120 member tribes and serve all 567 federally recognized tribes. Tribes are honored to serve as important partners of federal state and local agencies to protect ambient air quality, indoor air quality and mitigate climate change.

NTAA will be providing written comments to EPA on Executive Order 13777 enforcing the regulatory reform agenda by May 15th. While NTAA appreciates the opportunity to provide comments within the short timeframe allotted for this process, NTAA can only offer these general comments at this time.

Since 1984, EPA's policy of working with tribes has been based on close coordination in respect for travel self-determination and sovereignty consistent with EPA's policy for the administration of environmental programs on Indian reservation signed in 1984 by President Reagan and reaffirmed by every administrations since that time.

This policy directs EPA to work in close coordination with the tribes and respect travel determination and sovereignty. Therefore, in the spirit of EPA's existing policies, NTAA requests a government to government consultation with tribes so the EPA can hear from tribes directly on their perspectives related to E.O. 13777.

We encourage EPA to demonstrate this continued commitment to developing and enforcing strong air quality regulations based on sounds science as well as support sovereignty and self-determination of states, local governments and tribes to the appropriate and adequate allocation of funding for state, local and travel air programs.

In relation to air quality regulations, I offer this perspective from EPA's own data. Since EPA's creation in 1970 during the Nixon administration, the Clean Air Act has successfully reduced air pollution that impacts public health significantly.

Since 1980, aggregate emissions of criteria pollutants and air toxics have decreased by nearly 70 percent whole gross domestic product has grown by 153 percent, vehicle miles traveled have increased by 106 percent and our population has grown by 41 percent, all since 1980. Thank you for the opportunity to comment.

Andrea Drinkard: Thank you, Andy. Operator, next line, please?

Operator: Our next comment comes from the line of Katie Huffling with Alliance of Nurses.

Katie Huffling: Hi, thank you, good afternoon. My name is Katie Huffling and I'm the Executive Director of the Alliance of Nurses for Healthy Environments. We're the only national nursing organization focusing solely on the environment and health.

We would like to express our strong support for ensuring that healthy protective regulations which is the Clean Air Act are kept in place. Evidence has shown that the Clean Air Act and accompanying regulations have contributed to reductions in air pollution resulting in prevention of over 160,000 premature deaths yearly as well as other adverse health outcomes such as heart attacks, asthma attacks and hospital admissions.

Repealing or modifying regulations showed to improve health and save lives, will contribute to undue harm to the public especially to our most vulnerable populations such as pregnant women and children.

As a nurse and midwife, my goal is to help women and families have the healthiest pregnancies possible. Fortunately, air pollution and ground level

ozone can present a challenge for women and children who are especially sensitive to the negative impacts of these pollutants.

I've seen firsthand how poor air quality days can have a significant effect on the health of pregnant women. Many times, my asthmatic patients would come into my office wheezing or report increased use of their inhalers on poor air quality days.

Having good control of asthma is an essential part of a healthy pregnancy as the mother's breasts are the baby's only source of oxygen.

We caution pregnant women to stay inside in poor air quality days as exposure to air pollution has been linked to poor pregnancy outcomes, exacerbation of asthma and lung irritation. Exposure to particulate matter during pregnancy is linked to pre-term birth, low birth weight and small for gestational age infants.

These adverse birth outcomes are serious conditions that can lead to a variety of short and long-term health impacts for the baby, and greater risk of chronic disease as an adult such as diabetes, high blood pressure and obesity.

We are also seeing long-term changes in the lungs of children whose mothers were exposed to higher levels of air pollution while pregnant. These changes can lead to an increased risk of asthma and decreased lung function in these children.

The financial implications of treating adverse birth outcomes and chronic illness across the lifespan, their (cause) are worsened by air pollution, should be accounted for when determining the cost effectiveness, the necessity of implementing regulations.

The total annual cost of treating asthma alone is estimated at more than $56 billion. The direct benefits of implementing clean air programs has vastly exceeded cost of implementation assuming health outcomes and contributing

to a stronger economy by preventing millions of lost workdays and increasing work productivity.

Regulations that ensure clean air for all Americans are essentially to save lives and protect health. That's why the Alliance of Nurses for Healthy Environments supports ensuring strong clean air regulations are continued. Thank you for this opportunity to comment today and I urge the EPA to continue to safeguard these health protective regulations.

Andrea Drinkard: Thank you, Katie. We're getting very close to the end of our call. I think we'll probably have time for about two to three more speakers. Operator, would you open the next line, please?

Operator: Our next comment comes from the line of Theodora Birdbear with Fort Berthold POWER.

Theodora Birdbear: Hello. My name is Theodora Birdbear. I'm a member of Fort Berthold POWER which stands for Protectors of Water & Earth Rights. I'm a tribal member living on the Fort Berthold Indian Reservation in Western North Dakota in the Bakken oilfields.

We, tribal members, are directly affected by the EPA's air and radiation regulations for the industry. And I object to any weakening of EPA;s air and radiation rules. I live in Mandaree which is targeted for the unconventional oil and gas drilling, fracking and flaring.

For the last nine years, these flaring and leaky wells have been placed by -- within 500 feet or less to tribal homes including near very young children who live in those homes. This is a public health issue.

There are more than 1,000 flaring wells within Fort Berthold boundaries and another 1,500 wells are planned or expected right now. And for the last nine years, tons of extracted natural gas which includes the greenhouse gas methane has been dumped directly into the air that we breathe on Fort Berthold Indian Reservation.

The EPA's air quality rules are critically important to the public health and safety of tribal members on the Fort Berthold Indian Reservation and must be strengthened, not weakened, air quality enforcement must also be strengthened anywhere in Indian country including on Fort Berthold.

So, EPA, I'm asking you to don't cater to the oil and gas industry by weakening your air quality regulations, protect the public health of all including we, trial members, on the Fort Berthold Indian Reservation. I will be submitting written comments also. Thank you.

Andrea Drinkard: Thank you, Theodora. Operator, next -- why don't you open the next line, please?

Operator: Our next comment comes from the line of (Joanna Malk) with (Newmant Mini). (Joanna), your line is open. You may be on mute. (Joanna), your line is open. You may be on mute.

Andrea Drinkard: Operator, we can go to the next line, please.

Operator: Our next comment comes from the line of (Mark Kragel) with Vanguard Natural Resources.

(Mark Kragel): Yes, this is (Mark Kragel) with Vanguard Natural Resources, an oil and gas acquisition company, and I would like to encourage the EPA to relax the bureau of land management's methane standards which is putting a very undue burden on very small wells -- oil and gas wells where the cost to recover the methane would be far more than cost to sell the oil and gas. So, that's my comment, thank you.

Andrea Drinkard: Thank you very much, (Mark). Operator, next line, please?

Operator: Our next comment comes from the line of Theodora Scarato, Environmental Health.

Theodora Scarato: Hi. The Environmental Health Trust is a scientific organization conducting research -- can you hear me.

Female: I lost signal.

Theodora Scarato: Hello?

Andrea Drinkard: Yes, we can hear you.

Theodora Scarato: Hello?

Andrea Drinkard: We can hear you. We can hear you.

Theodora Scarato: OK. The Environmental Health Trust is a scientific organization conducting research on environmental health risks and prevention. We ask the EPA to update their public recommendations on non-ionizing electromagnetic radiation to fully inform the public about the current best available science and how to fully reduce exposure from the technology devices we use every day.

Since the World Health Organization's international agency with the research on cancer classified radiofrequency, radiation is a class 2B carcinogen (and 211) and evidence has significantly increased, showing the long-term radiofrequency radiation could cause cancer.

A recent animal study performed by the National Toxicology Program in the United States found an increased incidence of cancer and increased DNA damage in rats with prolonged exposure to radiofrequency fields.

They were said to mimic a lifetime of wireless exposure. Importantly, these adverse effects occurred at levels below those that caused thermal injury. Therefore, FCC regulations which are only based on thermal effects do not provide adequate protection for the public as stated by the California Medical Association in their wireless resolution in 2014.

Peer reviewed research has demonstrated adverse biological effects of wireless EMF including single and double stranded DNA breaks, creation of reactive oxygen species, immune dysfunction, cognitive processing effects, stress protein synthesis in the brain, altered brain development, sleep and

memory disturbances, ADHD, abnormal behavior, sperm dysfunction, and brain tumors.

The EPA needs to inform the public that cell phones and wireless devices were never premarket tested for long-term safety. Substantial peer reviewed research indicates not only cancer but also adverse effects to the brain and reproductive system from wireless radiation.

Over a dozen governments such as France, Belgium and Israel have online public resource specifically recommending that children's exposure be minimized. And their governments provide very details resources detailing how you can reduce exposure with everything from cell phones to baby monitors to laptops. We don't have that in the EPA. There were only three lines of texts on this.

The American Academy of Pediatrics now recommends that children's exposure to cell phones be reduced and specifies steps parents can take to reduce exposure such as make only short or essential calls on the cell phones, avoid carrying the phone against your body like in a pocket, sock or bra because cell phone manufacturers can't guarantee that the amount of radiation you're absorbing will be at the safe level.

In fact, people are likely absorbing radiation levels higher than government standards because before phones and wireless devices came in the market, their radiation tested at distances away from the body, not against the body.

So, for example, many cells phones are tested in about half an inch or less.

Andrea Drinkard: Thanks, Theodora. Your time is up. Operator, would you, please, open the last line. We'll have one more commenter today. Thank you.

Operator: And our final comment comes from the line of (Ernest Erlemond) with Earthjustice.

(Ernest Erlemond): Thank you. Please wake up, I know it's been a long day. Houses in cities are being photographed in gulf and wood smoke. While the (DHHS)

and everyone else proclaims that there is no safe level of any kind of smoke because…

(Off-Mic)

(Ernest Erlemond): …such as asthma attacks, heart attacks, cancer and so on.

Obviously, the Clean Air Act is not protecting…

(Off-Mic)

(Ernest Erlemond): And safety as required by the law. So, please revise it. Every revision so far has been much better than the original, which itself was good.

And excuse me for getting technical here, but average P.M. 2.5 from visibility maps converted to P.M. 2.5 maps is about 15 micrograms per cubic meter in most places. And the toxic equivalent is 150 micrograms per cubic meter because 50 percent of it is wood smoke.

So, please prevent the hotspot pollution in houses and you will prevent most regional air pollution problems like the problems in Fairbanks. Please ban all fireplaces and stoves from burning (core wood) in neighborhoods like London banned coal burning in fireplaces unless it can be proved safe. Thank you for allowing me to speak.

Andrea Drinkard: Thank you, (Ernest). And thank you, everyone, for joining us today. We appreciate all of your inputs. Again, if you did not have the opportunity to speak on today's call or if you had additional comments that you'd like to provide, please submit your input to the EPA (Why) docket. Again, that number is EPA-HQ-OA-2017-0190. Thank you again and have a great day.

Operator: This concludes today's conference call. You may now disconnect your lines.

END

Message

**From**: Woods, Clint [woods.clint@epa.gov]
**Sent**: 11/20/2018 5:34:40 PM
**To**: Konkus, John [konkus.john@epa.gov]; Harlow, David [harlow.david@epa.gov]
**Subject**: Fwd: Ed Calabrese

Begin forwarded message:

**From:** "Rust, Susanne" <susanne.rust@latimes.com>
**Date:** November 20, 2018 at 12:23:45 PM EST
**To:** "woods.clint@epa.gov" <woods.clint@epa.gov>
**Subject: Ed Calabrese**

Dear Mr Woods,

I'm a reporter at the Los Angeles Times working on a story about hormesis, Ed Calabrese, LNT and the EPA's proposed new rule on transparency in science.
I came across some emails you exchanged with Dr. Calabrese this spring about LNT. According to the chronology, you sought Calabrese's advice on what to incorporate into the rule, you spoke, and he also provided you with language to use, which was then incorporated into the rule - word-for-word.
I wonder if you could answer some questions about this exchange for me?

1) Who suggested you contact Calabrese?
2) What other toxicologists/scientists did you consult with?
3) In one of your emails, you mentioned that you and Calabrese had known one another years ago. Can you tell me how?

Thanks for your time. Feel free to call me at: Ex. 6 Personal Privacy (PP)

Susanne Rust

Reporter, The Los Angeles Times
Ex. 6 Personal Privacy (PP)

Message

**From:** Hewitt, James [hewitt.james@epa.gov]
**Sent:** 2/19/2019 1:46:07 PM
**To:** Block, Molly [block.molly@epa.gov]; Abboud, Michael [abboud.michael@epa.gov]; Konkus, John [konkus.john@epa.gov]; Beach, Christopher [beach.christopher@epa.gov]; McFaul, Jessica [mcfaul.jessica@epa.gov]; Woods, Clint [woods.clint@epa.gov]
**Subject:** RE: LA Times: Scientist says some pollution is good for you — a disputed claim Trump's EPA has embraced

Call her out.

**From:** Block, Molly
**Sent:** Tuesday, February 19, 2019 8:43 AM
**To:** Hewitt, James <hewitt.james@epa.gov>; Abboud, Michael <abboud.michael@epa.gov>; Konkus, John <konkus.john@epa.gov>; Beach, Christopher <beach.christopher@epa.gov>; McFaul, Jessica <mcfaul.jessica@epa.gov>; Woods, Clint <woods.Clint@epa.gov>
**Subject:** LA Times: Scientist says some pollution is good for you — a disputed claim Trump's EPA has embraced

# Ex. 5 Deliberative Process (DP)

Also, it's really embarrassing for the LA Times to call the head of the EPA Secretary. She refers to Secretary Pruitt below in the article. Technically, he doesn't exist… but seriously, how can you get the title wrong for the head of a major federal agency when you've been supposedly working on this article for months now?

Molly

**LA Times**
**Scientist says some pollution is good for you — a disputed claim Trump's EPA has embraced**
**https://www.latimes.com/local/california/la-me-secret-science-20190219-story.html**
Susanne Rust

Water samples are taken for testing from a canal in the Cawelo Water District near Bakersfield in 2015. A researcher who has suggested that exposure to toxic chemicals can be good for humans is helping to shape Environmental Protection Agency policies. (Brian van der Brug / Los Angeles Times)

In early 2018, a deputy assistant administrator in the EPA, Clint Woods, reached out to a Massachusetts toxicologist best known for pushing a public health standard suggesting that low levels of toxic chemicals and radiation are good for people.

"I wanted to check to see if you might have some time in the next couple of days for a quick call to discuss a couple items …," Woods wrote to Ed Calabrese.

Less than two weeks later, Calabrese's suggestions on how the EPA should assess toxic chemicals and radiation were introduced, nearly word for word, in the U.S. government's official journal, the Federal Register.

"This is a major big time victory," Calabrese wrote in an email to Steve Milloy, a former coal and tobacco lobbyist who runs a website, junkscience.com, that seeks to discredit mainstream climate science.

"Yes. It is YUGE!" wrote Milloy, in response.

It was a glorious moment for Calabrese, who had been snubbed for decades by mainstream public health scientists because of his controversial research and theories.

It also signified the major shift the EPA has taken under the Trump administration. More than any before it, this White House has actively sought out advice from industry lobbyists and the scientists they commission in setting pollution rules.

Denouncing the Obama-era EPA as an agency beholden to environmental extremists, the administration has not only dismissed mainstream science but embraced widely discredited alternatives that critics say are not consistent with the agency's focus on improving public and environmental health.

Calabrese's role illustrates a different side of this shift: the potential removal of longstanding public health practices and the incorporation of industry-backed and disputed science into federal environmental policy.

Calabrese spent decades advancing his ideas, facing skepticism and criticism from peers in the toxicology community while winning funding from companies whose bottom lines conformed with his views.

He says most of the pushback he receives comes from left-of-center toxicologists who see him as "the devil incarnate" for accepting industry funding and challenging their ideology. He maintains his science is solid and will be vindicated in time.

"These environmental regulatory people are very closed-minded," he said. They won't reconsider their standards, and see that some of the agents they call harmful "actually can induce adaptive responses," Calabrese said.

This view — that pollution and radiation can be beneficial — has many experts worried. The fact that such a position may become EPA policy, they say, portends a future in which corporate desires outweigh public and environmental health.

"Industry has been pushing for this for a long time," said David Michaels, former assistant secretary of labor for the Occupational Safety and Health Administration who's a professor of environmental and occupational health at George Washington University. "Not just the chemical industry, but the radiation and tobacco industries too."

If the EPA ultimately adopts Calabrese's proposed new regulations, researchers say it could change decades of standards and guidelines on clean air, water and toxic waste. It could also fundamentally alter the way the government assesses new chemicals and pesticides entering the marketplace.

"This is industry's holy grail," said Michaels.

**Can pollution be healthy?**

For decades, federal agencies charged with investigating and regulating carcinogens, toxic chemicals and radiation have been guided by the assumption that if a substance is dangerous at some level, it is harmful at any level. The higher the exposure, the more harm done. The lower the dose, the less. And the risk doesn't entirely disappear until the substance is removed.

This is known as the linear no-threshold model, and industry dislikes it because it generally assumes that there is no level, or threshold, of exposure that can be considered totally safe.

But research done on low exposures to toxins has been less than definitive. Experiments designed to test carcinogens and radiation at low levels often produce conflicting results — with, for example, some studies of a

chemical showing harm, other studies showing no effect, and a few suggesting a net benefit. In other cases, there is no information at all to guide regulators.

In the face of such uncertainty, the EPA and other agencies have taken a cautious approach by relying on the linear no-threshold model. Where data are absent or uncertain, they assume some level of risk.

It is an imperfect but protective approach, say many public health specialists. They argue that in a human population that varies widely in age, health and levels of chemical exposures, it is imperative that the agency cast a wide, conservative and protective net.

For decades, national and international scientific bodies have upheld this approach. It has been reviewed and re-reviewed dozens of times, including most recently by the congressionally chartered National Council on Radiation Protection and Measurements, the National Academy of Sciences, Engineering and Medicine and the EPA.

At the same time, industry has funded scientists to conduct and promote research designed to poke holes in the linear no-threshold model.

And that is where Calabrese comes in. He has long argued that regulators "erred on the side of being protective" at the cost of billions of dollars per year to industry.

Calabrese is a proselytizer of hormesis, the idea that dangerous chemicals and radiation are beneficial at low doses. He says they have a stimulating effect.

Polluting industries have promoted hormesis as an alternative to linear no-threshold for decades, but they had gotten little traction until the EPA embraced it last April.

"It's clearly not mainstream," said Thomas Burke, professor and director of the Risk Sciences Institute at Johns Hopkins' Bloomberg School of Public Health.

Burke and other experts say there are clearly scenarios where toxic chemicals can have beneficial effects in clinical and pharmacological settings, such as in the case of tamoxifen, which at low doses is effective at preventing and treating breast cancer but at higher doses can lead to blood clots, stroke and uterine cancer.

But, they say, what happens in a clinical setting can't and shouldn't be immediately applied to a regulatory, public health setting.

In the clinical case, "you have a doctor controlling and administering the medication to an individual," said David Jacobs, a professor of public health at the University of Minnesota, who has published studies showing hormetic effects in some industrial pollutants. "The doctor can pull the medication at any time."

"There is no way to control the dose a person gets from an industrial or agricultural chemical," he said. "It's not being doled out in pills and monitored by a physician who can lower it if the patient isn't responding well."

Therefore, Jacobs said, it would be dangerous to use hormesis as a framework for protecting public and environmental health.

"It really doesn't pass the sniff test" when applying it to public health, Burke said, while allowing for its place in the forum of ideas. "I always teach my classes that there are other theories. It's like any part of science, there are different points of view. Whether it's about climate change or low doses."

But he also teaches that one needs to know who has skin in the game. And in the case of hormesis, he said, that's industry.

**Big Tobacco embraces disputed research**

In the early 1980s, Calabrese was a tenured professor at the University of Massachusetts, stringing together public agency and industry-funded grants to study chemicals in drinking water and the effects of ozone on mice.

His funders included the EPA, the state of Massachusetts, the Hoffman-LaRoche pharmaceutical company and semiconductor giant Digital Corp.

Then in 1985, he reached out to the Council for Tobacco Research, the research arm of the tobacco industry, seeking a grant to examine "a possible inherited and metabolic susceptibility to lung cancer in smokers." His proposal was declined.

Sheldon Sommers, a physician at New York's Lenox Hill Hospital and scientific director of the council, wrote in response to the grant application that Calabrese's proposal "... is a mad hatter's tea party sort of epidemiologic approach, and a total $2.1 million plus would likely be frittered away in my opinion," according to documents from the UC San Francisco Truth Tobacco Industry Documents archive.

But by the 1990s, Calabrese had solidly established himself as a trusted scientist with the tobacco industry. He found they were interested in research that questioned the methods that regulatory agencies use to assess risk.

In a 1994 proposal to R.J. Reynolds, Calabrese offered to investigate a new kind of smokeless cigarette for the company, but also incorporate into his research "the loss of current benefits associated with smoking, such as protection from certain types of cancers and other illnesses…"

It was when he began his work on hormesis that Calabrese got attention from a broader range of industries.

With seed money from R.J. Reynolds, Dow Chemical, Procter & Gamble and others, as well as the EPA, Calabrese established a hormesis working group at the University of Massachusetts, which he called the Biological Effects of Low Level Exposures, or BELLE. Minutes from a 1990 advisory board meeting show the group chose not to use the word "hormesis" in its official name.

According to documents, Calabrese and his funders also held off on pushing a hormesis regulatory agenda until they'd built a sizable base of published scientific research.

Between 1990 and 2013, Calabrese received more than $8 million from companies and institutions, including R.J. Reynolds, Exxon Mobil, Dow Chemical, General Electric, the Department of Energy and the U.S. Air Force, to conduct research on hormesis.

Spokesmen from Exxon Mobil and the Air Force say they no longer fund Calabrese's work.

Calabrese established his own scientific society, the International Dose Response Society, and his own hormesis journal — now called Dose Response — where he served as editor-in-chief.

He wrote hundreds of articles, in his own journal and in others (including "Should hormesis be the default model in risk assessment?" and "The importance of hormesis to public health"), organized dozens of conferences and delivered scores of talks.

And while his publication portfolio is vast, it is also broad. It includes not just studies of hormesis, but research on soil ingestion, opinion pieces on law and regulatory policy, historical treatise on science, and a few scathing, posthumous rebukes of revered scientists, such as Herman Muller, a Nobel prize-winner and supporter of linear no-threshold.

Calabrese insists his funding does not influence his work.

"My job involves finding financial support to do studies in my field," said Calabrese. "I seek support from the private and public sectors. The University independently evaluates each of these for compliance with the rules."

Not all of his money comes from industry or government agencies with extensive toxic waste sites. Between 2000 and 2013, Calabrese received $50,000 from the EPA to hold a conference on soil ingestion, and $50,000 from CalEPA for a reference database he built on cancer publications. He also received a $750,000 joint grant from the EPA and the American Chemistry Council, the chemical industry's trade group, to study soil ingestion by construction workers.

Yet, despite his prolific career, he has instigated criticism and rebuke from many of his peers for his push on public and environmental health policy. He has been described as a "prominent industry consultant," having "outlying views," whose science is "way out there."

For years he failed to get regulatory agencies to take him seriously.

Then Donald Trump was elected president.

On Sept. 5, 2017, nearly nine months after Trump was sworn in as president and seven months after Scott Pruitt was confirmed as head of the EPA, Calabrese wrote an email to Milloy, the former coal lobbyist who is a Fox news commentator. The Los Angeles Times obtained the emails through a public records request to the University of Massachusetts.

"I wanted to connect with you on whether and how it may be possible to get the EPA to consider changing the LNT [linear no-threshold model] to something far better," Calabrese wrote.

Milloy had served on Trump's EPA transition team and was still in touch with high-ranking officials in then Secretary Pruitt's agency.

A few months later, Calabrese wrote to Milloy again, letting him know that he'd corresponded with Ryan Jackson, Pruitt's chief of staff, and sensed interest in a move against linear no-threshold.

Not long after Woods, the EPA's deputy assistant of the Office of Air and Radiation, emailed Calabrese asking if he wanted to talk about "default linear assumptions" and other items.

The two arranged a call, and on April 19, 2018, Woods sent Calabrese draft language for a small section in the EPA's proposed new ruling on transparency, called "Strengthening Transparency in Regulatory Science."

"It is good what you have but you need a little more," wrote Calabrese, who then suggested a line, which he altered twice, in email exchanges with Woods, before settling on this: "EPA shall also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on the major competing models (LNT, Threshold, and Hormesis)."

In other words, if the EPA is uncertain about a particular chemical's impacts at low doses, it would abandon linear no-threshold as a default, and try other models instead, including hormesis.

On April 25, Milloy sent Calabrese the final wording for the draft proposal, which included Calabrese's line nearly word for word.

"I am almost passing out with surprise and euphoria… " Calabrese wrote Milloy after seeing the document.

The rule was posted for comment in the Federal Register on April 30, although a final ruling has not been announced.

John Konkus, an EPA spokesman, said the input and perspective from "the Editor-in-Chief of the journal, Dose Response" was welcomed, and reflected the perspective of "a wide variety of scientific experts" the agency reached out to when drafting the proposal.

Public health specialists outside the agency say that if the final language is adopted, it is likely to tie the EPA up in knots as it tries and then debates all the alternative models. It could also have profound effects on current and future standards for drinking water, air and toxic waste sites.

"EPA tries to be conservative in its setting of risks," said Jan Beyea, a retired radiation physicist who has worked with the National Academies of Science. "Calabrese and collaborators think that most pollutants are good for you at low doses, so no need to be conservative."

EPA spokeswoman Molly Block declined to speculate on whether the rule would be passed and how it would affect environmental rules that were set based on the linear no-threshold model.

Industry groups have praised the proposed change.

"We support moving away from over-reliance on the linear no -threshold default," wrote a spokesman for the American Chemistry Council, the trade group for the chemical industry. It's a method, he says that "frequently results in inflated health risk estimates and unwarranted, costly risk management decisions."

Milloy also seemed pleased with the proposed ruling.

"The EPA should be open and transparent about how and what they are basing their decisions on," he said, "and they should be using the best science available."

In any case, he said, "we're winning."

Message

**From:** Block, Molly [block.molly@epa.gov]
**Sent:** 2/17/2019 12:44:36 AM
**To:** Abboud, Michael [abboud.michael@epa.gov]
**CC:** Hewitt, James [hewitt.james@epa.gov]; Konkus, John [konkus.john@epa.gov]; McFaul, Jessica [mcfaul.jessica@epa.gov]
**Subject:** Re: Story on Calabrese

FYI-

Hi,

They're holding til later in the week.

---

**From:** Rust, Susanne
**Sent:** Saturday, February 16, 2019 5:57 AM
**To:** Konkus, John; Block, Molly
**Subject:** LNT/ hormesis story

Hi John and Molly,

I wanted to let you both know the story is slated to run tomorrow.
I'll send a link when it goes live.
Thanks for your help. Susanne

Reporter, The Los Angeles Times
Ex. 6 Personal Privacy (PP)

Sent from my iPhone

On Feb 16, 2019, at 11:23 AM, Block, Molly <block.molly@epa.gov> wrote:

> Here's the back and forth from 2/5
>
> OK. Thanks.
>
> ---
>
> **From:** Block, Molly <block.molly@epa.gov>
> **Sent:** Tuesday, February 5, 2019 1:27 PM
> **To:** Rust, Susanne
> **Cc:** Press
> **Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request
>
> EXTERNAL SOURCE
> Hi Susanne –
>
> On background: That's not true. The Agency did not approach him twice to direct ORD nor did he turn down an invitation to meet about serving in some capacity at EPA.

EPA has a number of advisory boards and science panels that he came in to talk about that. He was actually recommended to a number of employees at the Agency.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Tuesday, February 5, 2019 4:02 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi Molly,

Sorry about the long break, there. I'm back on the story.
Couple things I'd like to verify:
Ed Calabrese said he'd been approached twice by the EPA to direct ORD. He said he turned down the invitation both times. Once in Jan 2017, the next time was in June or July of 2017.
Can you confirm or dispute this?
Thanks,
Susanne Rust

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 12:38 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

As we've previously stated: You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on these issues, and EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:16 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 11:15:28 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

I should have something for you shortly.

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:13 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

Would it be fair to say the EPA declined to comment on Milloy and Calabrese's influence on the proposed ruling? Or will you have a response.
Thank you.
Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 7:24:49 AM
**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

I have information suggesting that Steve Milloy and Edward Calabrese were instrumental in crafting the ruling's suggestion to incorporate risk models other than LNT.
I wonder if you could tell me what their role was in crafting the rule and and who solicited their input?
Thank you.
Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 6:27:41 AM
**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Understood. Still wondering when a final ruling or decision is expected?

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 6:27:01 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

As we've stated before, we are currently reviewing 590,000 public comments on the proposal.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 9:26 AM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi -

Any idea when the EPA will make a decision or submit a final ruling?
Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 1:14:50 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

This should be helpful for you:

The proposed regulation takes comment on ensuring transparency and consideration of high quality studies evaluating models and model assumptions, including high quality studies that examine different potential dose-response relationships. You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on particular studies, and the EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Wednesday, November 7, 2018 3:18 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi

Ha. No. I'm not suggesting any new models. Just wondering what this is based on and why it's being incorporated? There's a discussion in the ruling about doubts re linearity non threshold models, and I'm curious about it's origin and why it's included in a ruling that seems to be mostly about transparency and open data? And what this would mean for the way EPA evaluates an performs risk assessments?
Thanks. Susanne

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 11:58 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

Do you have specific questions? Or are you interested in any specific models? The transparency rule does not ask for the public to suggest or otherwise comment on "new models to evaluate risk assessment."

I'm happy to help, just trying to figure out the best way to answer your inquiry.

Molly

Begin forwarded message:

> **From:** "Rust, Susanne" <susanne.rust@latimes.com>
> **Date:** November 7, 2018 at 8:37:03 AM EST
> **To:** "daguillard.robert@epa.gov" <daguillard.robert@epa.gov>
> **Subject: Strengthening Transparency in Regulatory Science/ Media request**
>
> Dear Mr. Daguillard,
>
> I am working on a story about the "Strengthening Transparency in Regulatory Science" proposal and I am hoping I can get some information and maybe a comment?
> I am particularly interested in the proposed rule's request for new models to evaluate risk assessment.
> Any chance you can talk today? Or can you put me in touch with someone who can tell me how this came about and why? My deadline is tomorrow at noon.
> Thank you.
> Susanne Rust
>
> Reporter, Los Angeles Times
> Ex. 6 Personal Privacy (PP)

Sent from my iPhone

On Feb 16, 2019, at 11:08 AM, Abboud, Michael <abboud.michael@epa.gov> wrote:

> Oh yeah she already sent her over answers.
>
> Sent from my iPhone
>
> On Feb 16, 2019, at 12:04 PM, Hewitt, James <hewitt.james@epa.gov> wrote:
>
>> No idea. Molly had worked with an LA Times reporter on something else.
>>
>> Sent from my iPhone
>>
>> On Feb 16, 2019, at 11:54 AM, Abboud, Michael <abboud.michael@epa.gov> wrote:
>>
>>> Did we already provide statements on this?
>>>
>>> Sent from my iPhone
>>>
>>> Begin forwarded message:

**From:** "Woods, Clint" <woods.clint@epa.gov>
**Date:** February 16, 2019 at 11:14:10 AM EST
**To:** "Konkus, John" <konkus.john@epa.gov>, "Abboud, Michael" <abboud.michael@epa.gov>
**Subject: Fwd: Story on Calabrese**

Begin forwarded message:

> **From:** "Rust, Susanne" <susanne.rust@latimes.com>
> **Date:** February 16, 2019 at 8:58:17 AM EST
> **To:** "Woods, Clint" <woods.clint@epa.gov>
> **Subject: Story on Calabrese**
>
> HI,
>
> I wanted to let you know the story I contacted you about several weeks ago is slated to run tomorrow.
> I'll send a link when it goes live.
> THanks, Susanne
>
> Reporter, The Los Angeles Times
> Ex. 6 Personal Privacy (PP)

Message

**From**: Knickmeyer, Ellen [EKnickmeyer@ap.org]
**Sent**: 2/1/2019 5:55:20 PM
**To**: Konkus, John [konkus.john@epa.gov]; Press [Press@epa.gov]
**Subject**: RE: Brant Ulsh on Radiation Advisory Panel-comment for story on deadline

Hello,
I'm also mentioning in our story that FOIA records show Ryan Jackson had an appointment with Edward Calabrese on June 28, 2017. Can you discuss what that was about?
Thanks
Ellen

---

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Friday, February 01, 2019 9:55 AM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>; Press <Press@epa.gov>
**Subject:** RE: Brant Ulsh on Radiation Advisory Panel-comment for story on deadline

Ellen: Please reference our press release on this subject: https://www.epa.gov/newsreleases/epa-appoints-new-members-science-advisory-board-and-subcommittees

Thank you,

John

---

**From:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Sent:** Friday, February 1, 2019 9:44 AM
**To:** Press <Press@epa.gov>
**Subject:** Brant Ulsh on Radiation Advisory Panel-comment for story on deadline

Hi, there,
Doing a story this morning on the EPA naming Brant Ulsh, who argues for abandoning the LNT model for radiation, to head its Radiation Advisory Panel. Can you tell me the reason the EPA named a physicist who holds a minority view on radiation to lead the panel, and is the EPA considering changing its adherence to LNT?

Thanks,
Ellen
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From**: Block, Molly [block.molly@epa.gov]
**Sent**: 2/5/2019 9:27:52 PM
**To**: Rust, Susanne [susanne.rust@latimes.com]
**CC**: Press [Press@epa.gov]
**Subject**: RE: Strengthening Transparency in Regulatory Science/ Media request

Hi Susanne –

On background: That's not true. The Agency did not approach him twice to direct ORD nor did he turn down an invitation to meet about serving in some capacity at EPA.

EPA has a number of advisory boards and science panels that he came in to talk about that. He was actually recommended to a number of employees at the Agency.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Tuesday, February 5, 2019 4:02 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi Molly,

Sorry about the long break, there. I'm back on the story.
Couple things I'd like to verify:
Ed Calabrese said he'd been approached twice by the EPA to direct ORD. He said he turned down the invitation both times. Once in Jan 2017, the next time was in June or July of 2017.
Can you confirm or dispute this?
Thanks,
Susanne Rust

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 12:38 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

As we've previously stated: You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on these issues, and EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:16 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 11:15:28 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

I should have something for you shortly.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:13 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

Would it be fair to say the EPA declined to comment on Milloy and Calabrese's influence on the proposed ruling? Or will you have a response.

Thank you.

Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 7:24:49 AM
**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

I have information suggesting that Steve Milloy and Edward Calabrese were instrumental in crafting the ruling's suggestion to incorporate risk models other than LNT.

I wonder if you could tell me what their role was in crafting the rule and and who solicited their input?

Thank you.

Susanne

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 6:27:41 AM
**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Understood. Still wondering when a final ruling or decision is expected?

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 6:27:01 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

As we've stated before, we are currently reviewing 590,000 public comments on the proposal.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 9:26 AM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi -

Any idea when the EPA will make a decision or submit a final ruling?

Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 1:14:50 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

This should be helpful for you:

The proposed regulation takes comment on ensuring transparency and consideration of high quality studies evaluating models and model assumptions, including high quality studies that examine different potential dose-response relationships. You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on particular studies, and the EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Wednesday, November 7, 2018 3:18 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi

Ha. No. I'm not suggesting any new models. Just wondering what this is based on and why it's being incorporated? There's a discussion in the ruling about doubts re linearity non threshold models, and I'm curious about it's origin and why it's included in a ruling that seems to be mostly about transparency and open data? And what this would mean for the way EPA evaluates an performs risk assessments?

Thanks. Susanne

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 11:58 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

Do you have specific questions? Or are you interested in any specific models? The transparency rule does not ask for the public to suggest or otherwise comment on "new models to evaluate risk assessment."

I'm happy to help, just trying to figure out the best way to answer your inquiry.

Molly

Begin forwarded message:

> **From:** "Rust, Susanne" <susanne.rust@latimes.com>
> **Date:** November 7, 2018 at 8:37:03 AM EST
> **To:** "daguillard.robert@epa.gov" <daguillard.robert@epa.gov>
> **Subject: Strengthening Transparency in Regulatory Science/ Media request**
>
> Dear Mr. Daguillard,

I am working on a story about the "Strengthening Transparency in Regulatory Science" proposal and I am hoping I can get some information and maybe a comment?

I am particularly interested in the proposed rule's request for new models to evaluate risk assessment.

Any chance you can talk today? Or can you put me in touch with someone who can tell me how this came about and why? My deadline is tomorrow at noon.

Thank you.

Susanne Rust

Reporter, Los Angeles Times

Ex. 6 Personal Privacy (PP)

Message

**From**: Block, Molly [block.molly@epa.gov]
**Sent**: 2/5/2019 9:22:54 PM
**To**: Jackson, Ryan [jackson.ryan@epa.gov]
**CC**: Hewitt, James [hewitt.james@epa.gov]; Abboud, Michael [abboud.michael@epa.gov]; Konkus, John [konkus.john@epa.gov]; Beach, Christopher [beach.christopher@epa.gov]
**Subject**: RE: Strengthening Transparency in Regulatory Science/ Media request

**Ex. 5 Deliberative Process (DP)**

---

**From:** Jackson, Ryan
**Sent:** Tuesday, February 5, 2019 4:21 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Hewitt, James <hewitt.james@epa.gov>; Abboud, Michael <abboud.michael@epa.gov>; Konkus, John <konkus.john@epa.gov>; Beach, Christopher <beach.christopher@epa.gov>
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

# Ex. 5 Deliberative Process (DP)

---

**From:** Block, Molly
**Sent:** Tuesday, February 5, 2019 4:13 PM
**To:** Jackson, Ryan <jackson.ryan@epa.gov>
**Cc:** Hewitt, James <hewitt.james@epa.gov>; Abboud, Michael <abboud.michael@epa.gov>; Konkus, John <konkus.john@epa.gov>; Beach, Christopher <beach.christopher@epa.gov>
**Subject:** FW: Strengthening Transparency in Regulatory Science/ Media request

Flagging

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Tuesday, February 5, 2019 4:02 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi Molly,

Sorry about the long break, there. I'm back on the story.
Couple things I'd like to verify:
Ed Calabrese said he'd been approached twice by the EPA to direct ORD. He said he turned down the invitation both times. Once in Jan 2017, the next time was in June or July of 2017.
Can you confirm or dispute this?
Thanks,
Susanne Rust

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 12:38 PM
**To:** Rust, Susanne

**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

As we've previously stated: You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on these issues, and EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:16 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 11:15:28 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

I should have something for you shortly.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:13 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

Would it be fair to say the EPA declined to comment on Milloy and Calabrese's influence on the proposed ruling? Or will you have a response.

Thank you.

Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 7:24:49 AM
**To:** Block, Molly

**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

I have information suggesting that Steve Milloy and Edward Calabrese were instrumental in crafting the ruling's suggestion to incorporate risk models other than LNT.

I wonder if you could tell me what their role was in crafting the rule and and who solicited their input?

Thank you.

Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 6:27:41 AM
**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Understood. Still wondering when a final ruling or decision is expected?

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 6:27:01 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

As we've stated before, we are currently reviewing 590,000 public comments on the proposal.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 9:26 AM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi -

Any idea when the EPA will make a decision or submit a final ruling?

Thank you.

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 1:14:50 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

This should be helpful for you:

The proposed regulation takes comment on ensuring transparency and consideration of high quality studies evaluating models and model assumptions, including high quality studies that examine different potential dose-response relationships. You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on particular studies, and the EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Wednesday, November 7, 2018 3:18 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi

Ha. No. I'm not suggesting any new models. Just wondering what this is based on and why it's being incorporated? There's a discussion in the ruling about doubts re linearity non threshold models, and I'm curious about it's origin and why it's included in a ruling that seems to be mostly about transparency and open data? And what this would mean for the way EPA evaluates an performs risk assessments?

Thanks. Susanne

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 11:58 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

Do you have specific questions? Or are you interested in any specific models? The transparency rule does not ask for the public to suggest or otherwise comment on "new models to evaluate risk assessment."

I'm happy to help, just trying to figure out the best way to answer your inquiry.

Molly

Begin forwarded message:

**From:** "Rust, Susanne" <susanne.rust@latimes.com>
**Date:** November 7, 2018 at 8:37:03 AM EST
**To:** "daguillard.robert@epa.gov" <daguillard.robert@epa.gov>
**Subject: Strengthening Transparency in Regulatory Science/ Media request**

Dear Mr. Daguillard,

I am working on a story about the "Strengthening Transparency in Regulatory Science" proposal and I am hoping I can get some information and maybe a comment?

I am particularly interested in the proposed rule's request for new models to evaluate risk assessment.

Any chance you can talk today? Or can you put me in touch with someone who can tell me how this came about and why? My deadline is tomorrow at noon.

Thank you.

Susanne Rust

Reporter, Los Angeles Times

**Ex. 6 Personal Privacy (PP)**

Message

**From:** Zahra Hirji [zahra.hirji@buzzfeed.com]
**Sent:** 10/3/2018 12:03:24 PM
**To:** Konkus, John [konkus.john@epa.gov]; Press [Press@epa.gov]
**Subject:** Media Request: Question About Science Transparency Rule & Radiation Guidelines

Dear John Konkus,

I'm a reporter for BuzzFeed News covering EPA's science transparency rule, and I have a few questions about the impacts. Yesterday, the AP published a story suggesting the rule proposal could impact EPA's radiation guidelines. While it's true the rule proposal does not mention radiation or the guidelines specifically, it does mention opening the discussion on various models. (Here's a sentence from the docket page for the rule: "EPA shall evaluate the appropriateness of using default assumptions, including assumptions of a linear, no-threshold dose response, on a case-by-case basis.") Some scientists I've spoken to say it is possible reconsidering the linear non-threshold model and the radiation guidelines could be impacted by the larger rule proposal, even though it's not spelled out so clearly in the proposal -- and it appears some people have provided comments to the proposal on this subject.

Can you confirm the public comment period on the rule proposal asked for input on the types of models that dictate the EPA's radiation guidelines and could open the door to changing these guidelines down the road? And can you comment on why University of Massachusetts scientist Edward Calabrese is quoted in EPA's press release for the rule saying essentially just that?

I am on deadline, and am looking to publish a story ahead of today's Senate EPW hearing on the transparency rule (where Calabrese is one of three invited speakers) and available on my cell at Ex. 6 Personal Privacy (PP)

Best,
Zahra Hirji

--
Zahra Hirji
Reporter
BuzzFeed News
Office Ex. 6 Personal Privacy (PP)
Cell: (
Zahra.Hirji@buzzfeed.com
@zhirji28

Message

**From:** David Stevenson Ex. 6 Personal Privacy (PP)
**Sent:** 4/24/2018 8:18:43 PM
**To:** Press [Press@epa.gov]
**Subject:** RE: EPA Administrator Pruitt Proposes Rule To Strengthen Science Used InEPA Regulations

Woo Hoo! Finally!
David T. Stevenson
Director, Center for Energy Competitiveness
Caesar Rodney Institute
And EPA Transition Team Member

Sent from Mail for Windows 10

**From:** EPA Press Office
**Sent:** Tuesday, April 24, 2018 2:30 PM
**To:** davidstevenson@caesarrodney.org
**Subject:** EPA Administrator Pruitt Proposes Rule To Strengthen Science Used InEPA Regulations

U.S. ENVIRONMENTAL PROTECTION AGENCY
NEWS RELEASE
WWW.EPA.GOV/NEWSROOM

# EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

**WASHINGTON** (April 24, 2018) - Today, U.S. Environmental Protection Agency (EPA) Administrator Scott Pruitt signed a proposed rule to strengthen the science used in regulations issued by EPA. The rule will ensure that the regulatory science underlying Agency actions is fully transparent, and that underlying scientific information is publicly available in a manner sufficient for independent validation.

"The era of secret science at EPA is coming to an end," **said EPA Administrator Scott Pruitt**. "The ability to test, authenticate, and reproduce scientific findings is vital for the integrity of rulemaking process. Americans deserve to assess the legitimacy of the science underpinning EPA decisions that may impact their lives."

This proposed rule is in line with the scientific community's moves toward increased data sharing to address the "replication crisis"—a growing recognition that a significant proportion of published research may not be reproducible. The proposal is consistent with data access requirements for major scientific journals like *Science*, *Nature*, and

*Proceedings of the National Academy of Sciences* as well as recommendations from the Bipartisan Policy Center's Science for Policy Project and the Administrative Conference of the United States' Science in the Administrative Process Project.

The proposed rule builds upon President Trump's executive orders on regulatory reform and energy independence:

- **Executive Order 13777**, issued in March 2017, provides that regulatory reform efforts shall attempt to identify "those regulations that rely in whole or in part on data, information, or methods that are not publicly available or that are insufficiently transparent to meet the standard of reproducibility."
- **Executive Order 13783**, also issued in March 2017, provides that "It is the policy of the United States that necessary and appropriate environmental regulations comply with the law, are of greater benefit than cost, when permissible, achieve environmental improvements for the American people, and are developed through transparent processes that employ the best available peer-reviewed science and economics."

**Chairman Lamar Smith (R-TX)**: "Administrator Pruitt's announcement ensures that data will be secret no more. For too long, the EPA has issued rules and regulations based on data that has been withheld from the American people. It's likely that in the past, the data did not justify all regulations. Today, Administrator Pruitt rightfully is changing business as usual and putting a stop to hidden agendas."

**Senator Mike Rounds (R-SD)**: "Sound, reliable science is vital to helping us make important policy decisions that impact the health of American families and their livelihoods. Inserting new levels of transparency in the EPA rulemaking process will help make the agency more accountable to the American people and help everyone understand the impact of EPA's decisions. Today's directive is a significant step toward making sure these decisions are not made behind closed doors with information accessible only to those writing the regulations, but rather in the full view of those who will be affected."

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts**: "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process."

**Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the Journal *Risk Analysis***: "I believe that transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science. Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been

developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."

**Dr. Jason Scott Johnston, Director, Olin Law and Economics Program, University of Virginia School of Law**: "EPA's proposed rule, Strengthening Transparency in Regulatory Science, is badly needed "Best practice among peer-edited scientific journals is to require that data and statistical routines used in published papers be posted online and/or made publicly available. To apply the same standards to research that EPA says justify regulations affecting billions of dollars in economic activity and millions of human lives is essential for those regulations to truly be scientifically based."

**Bruno Pigott, Commissioner of the Indiana Department of Environmental Management (IDEM)**: "IDEM supports transparency in rulemaking. Good, sound science leads to better regulations."

**Dr. George Wolff, Principal Scientist, Air Improvement Resource, Inc., and former Chairman of EPA's Clean Air Scientific Advisory Committee (1992 – 1996)**: "In the development of regulations based on environmental studies, numerous subjective assumptions and choices must be made regarding the selection of data and models that have a profound impact on the strength of any statistical associations and even whether the associations are positive or negative. The appropriateness of the assumptions and choices are not adequately evaluated in the standard peer review process. That is why it is essential that the data and models be placed in the public domain for a more rigorous evaluation by qualified experts. The proposed regulation, Strengthening Transparency in Regulatory Science, will provide an opportunity for such evaluations."

###

Visit The EPA's Newsroom

U.S. Environmental Protection Agency
1200 Pennsylvania Avenue Northwest
Washington, D.C. 20004

Like
Tweet
Share
Forward

Unsubscribe

Message

**From**: Block, Molly [block.molly@epa.gov]
**Sent**: 4/24/2018 7:19:48 PM
**To**: Michael Ball [michael.ball@argusmedia.com]; Press [Press@epa.gov]
**Subject**: RE: EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations
**Attachments**: Strenthening Transparency in Regulatory Science 04-24-2018.pdf

See attached.

---

**From:** Michael Ball [mailto:michael.ball@argusmedia.com]
**Sent:** Tuesday, April 24, 2018 2:50 PM
**To:** Press <Press@epa.gov>
**Subject:** RE: EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

Is this proposed rule available online or via e-mail? Didn't see a link in the press release.

Thanks

Mike

Michael Ball
Air Daily Editor

www.argusmedia.com
Direct: Ex. 6 Personal Privacy (PP)
Email: michael.ball@argusmedia.com
Yahoo/Skype ID: argusball

www.argusmedia.com

Ex. 6 Personal Privacy (PP)
Argus Media Inc., 1667 K Street NW, Suite 1150, Washington, DC 20006

illuminating the markets

---

**From:** EPA Press Office [mailto:press=epa.gov@cmail19.com] **On Behalf Of** EPA Press Office
**Sent:** Tuesday, April 24, 2018 2:30 PM
**To:** Michael Ball <michael.ball@argusmedia.com>
**Subject:** EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

Notice: external email -- please use caution.

# EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

**WASHINGTON** (April 24, 2018) - Today, U.S. Environmental Protection Agency (EPA) Administrator Scott Pruitt signed a proposed rule to strengthen the science used in regulations issued by EPA. The rule will ensure that the regulatory science underlying Agency actions is fully transparent, and that underlying scientific information is publicly available in a manner sufficient for independent validation.

"The era of secret science at EPA is coming to an end," **said EPA Administrator Scott Pruitt**. "The ability to test, authenticate, and reproduce scientific findings is vital for the integrity of rulemaking process. Americans deserve to assess the legitimacy of the science underpinning EPA decisions that may impact their lives."

This proposed rule is in line with the scientific community's moves toward increased data sharing to address the "replication crisis"—a growing recognition that a significant proportion of published research may not be reproducible. The proposal is consistent with data access requirements for major scientific journals like *Science*, *Nature*, and *Proceedings of the National Academy of Sciences* as well as recommendations from the Bipartisan Policy Center's Science for Policy Project and the Administrative Conference of the United States' Science in the Administrative Process Project.

The proposed rule builds upon President Trump's executive orders on regulatory reform and energy independence:

- **Executive Order 13777**, issued in March 2017, provides that regulatory reform efforts shall attempt to identify "those regulations that rely in whole or in part on data, information, or methods that are not publicly available or that are insufficiently transparent to meet the standard of reproducibility."
- **Executive Order 13783**, also issued in March 2017, provides that "It is the policy of the United States that necessary and appropriate environmental regulations comply with the law, are of greater benefit than cost, when permissible, achieve environmental improvements for the American people, and are developed through transparent processes that employ the best available peer-reviewed science and economics."

**Chairman Lamar Smith (R-TX)**: "Administrator Pruitt's announcement ensures that data will be secret no more. For too long, the EPA has issued rules and regulations based on data that has been withheld from the American people. It's likely that in the past, the data did not justify all regulations. Today, Administrator Pruitt rightfully is changing business as usual and putting a stop to hidden agendas."

**Senator Mike Rounds (R-SD)**: "Sound, reliable science is vital to helping us make important policy decisions that impact the health of American families and their livelihoods. Inserting new levels of transparency in the EPA rulemaking process will help make the agency more accountable to the American people and help everyone understand the impact of EPA's decisions. Today's directive is a significant step toward making sure these decisions are not made behind closed doors with information accessible only to those writing the regulations, but rather in the full view of those who will be affected."

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts**: "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process."

**Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the Journal *Risk Analysis***: "I believe that

transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science. Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."

**Dr. Jason Scott Johnston, Director, Olin Law and Economics Program, University of Virginia School of Law**: "EPA's proposed rule, Strengthening Transparency in Regulatory Science, is badly needed "Best practice among peer-edited scientific journals is to require that data and statistical routines used in published papers be posted online and/or made publicly available. To apply the same standards to research that EPA says justify regulations affecting billions of dollars in economic activity and millions of human lives is essential for those regulations to truly be scientifically based."

**Bruno Pigott, Commissioner of the Indiana Department of Environmental Management (IDEM)**: "IDEM supports transparency in rulemaking. Good, sound science leads to better regulations."

**Dr. George Wolff, Principal Scientist, Air Improvement Resource, Inc., and former Chairman of EPA's Clean Air Scientific Advisory Committee (1992 – 1996)**: "In the development of regulations based on environmental studies, numerous subjective assumptions and choices must be made regarding the selection of data and models that have a profound impact on the strength of any statistical associations and even whether the associations are positive or negative. The appropriateness of the assumptions and choices are not adequately evaluated in the standard peer review process. That is why it is essential that the data and models be placed in the public domain for a more rigorous evaluation by qualified experts. The proposed regulation, Strengthening Transparency in Regulatory Science, will provide an opportunity for such evaluations."

###

Visit The EPA's Newsroom

U.S. Environmental Protection Agency
1200 Pennsylvania Avenue Northwest
Washington, D.C. 20004

Share
Forward

Unsubscribe

The information contained in this email and its attachments is confidential and may be the subject of professional or other privilege. It may not be disclosed to anyone else without consent from the Argus Media group. If you are not the intended recipient please notify the sender and destroy this email and its attachments immediately; please do not use, disclose, distribute, copy, print or rely on the contents of this email or its attachments. While the Argus Media group takes care to protect its systems from electronic virus attack or other harmful event, the Argus Media group gives no warranty that this email or its attachments are free of any virus or other harmful matter and accepts no responsibility for any loss or damage resulting from the recipient receiving, opening or using it or its attachments. Email is not a secure method of communication and email messages may be intercepted. Messages sent to and from the Argus Media group may be monitored, reviewed and/or processed in accordance with the Argus Media group's policies, including for the purpose of ensuring compliance with legal and regulatory obligations. Translations of this email disclaimer are available in Japanese, Mandarin, German, Portuguese and Russian at www.argusmedia.com/disclaimer.
Argus Media Limited has moved offices. Please note our new address below.

Argus Media Limited, Lacon House, 84 Theobald's Road, London WC1X 8NL Registered in England and Wales, Company Registration No: 1642534 VAT Registration No: GB 229 7149 41

**ENVIRONMENTAL PROTECTION AGENCY**

**40 CFR Part 30**

**[EPA-HQ-OA-2018-0259; FRL-XXXX-XX]**

**RIN 2080-AA14**

**Strengthening Transparency in Regulatory Science**

**AGENCY:** Environmental Protection Agency (EPA).

**ACTION:** Proposed rule.

**SUMMARY:** This document proposes a regulation intended to strengthen the transparency of EPA regulatory science. The proposed regulation provides that when EPA develops regulations, including regulations for which the public is likely to bear the cost of compliance, with regard to those scientific studies that are pivotal to the action being taken, EPA should ensure that the data underlying those are publicly available in a manner sufficient for independent validation. In this notice, EPA solicits comment on this proposal and how it can best be promulgated and implemented in light of existing law and prior Federal policies that already require increasing public access to data and influential scientific information used to inform federal regulation.

**DATES:** Comments must be received on or before **[insert date 30 days after date of publication in the Federal Register]**.

**ADDRESSES:** Submit your comments, identified by Docket ID No. EPA–HQ–OA-2018-0259, at *https:// www.regulations.gov*. Follow the online instructions for submitting comments. Once submitted, comments cannot be edited or removed from *Regulations.gov*. EPA may publish any comment received to its public docket. Do not submit electronically any information you consider to be Confidential Business Information (CBI) or other information whose disclosure is restricted by statute. Multimedia submissions (audio, video, etc.) must be accompanied by a



ED_002751_00006736-00001

written comment. The written comment is considered the official comment and should include discussion of all points you wish to make. EPA will generally not consider comments or comment contents located outside of the primary submission (*i.e.*, on the web, cloud, or other file sharing system). For additional submission methods, the full EPA public comment policy, information about CBI or multimedia submissions, and general guidance on making effective comments, please visit *https://www.epa.gov/dockets/ commenting-epa-dockets.*

**FOR FURTHER INFORMATION, CONTACT:** Tom Sinks, Office of the Science Advisor, Environmental Protection Agency, 1200 Pennsylvania Avenue NW, Washington, DC 20460; (202) 564-0221; email address: *staff_osa@epa.gov*.

**SUPPLEMENTARY INFORMATION:**

*Submitting CBI.* Do not submit information that you consider to be CBI electronically through *https://www.regulations.gov* or email. Send or deliver information identified as CBI to only the following address using U.S Postal Service: U.S. Environmental Protection Agency, EPA Docket Center, EPA–HQ–OA-2018-0259, Mail Code 28221T, 1200 Pennsylvania Avenue, NW, Washington, DC 20460. For other methods of delivery, see https://www.epa.gov/dockets/where-send-comments-epa-dockets.

Clearly mark the part or all of the information that you claim to be CBI. For CBI information in a disk or CD-ROM that you mail to EPA, mark the outside of the disk or CD-ROM as CBI and then identify electronically within the disk or CD-ROM the specific information that is claimed as CBI. In addition to one complete version of the comment that



ED_002751_00006736-00002

includes information claimed as CBI, a copy of the comment that does not contain the information claimed as CBI must be submitted for inclusion in the public docket. If you submit a CD-ROM or disk that does not contain CBI, mark the outside of the disk or CD-ROM clearly that it does not contain CBI. Information marked as CBI will not be disclosed except in accordance with procedures set forth in 40 Code of Federal Regulations (CFR) part 2.

*Organization of This Document*. The following outline is provided to aid in locating information in this preamble.


I. General Information

A. Does this Action Apply to Me?

B. What action is the Agency taking?

C. What is the Agency's Authority for taking this action?

II. Background

III. Request for Comment

IV. Statutory and Executive Orders


## I. General Information

### *A. Does this action apply to me?*

This proposed regulation does not directly regulate any entity outside the federal government. However, any entity interested in EPA's regulations may be interested in this proposal. This proposal may be of particular interest to entities that conduct research and other scientific activity that is likely to be relevant to EPA's regulatory activity.



ED_002751_00006736-00003

*B. What action is the agency taking?*

This notice solicits information and comment from the public on a proposed regulation intended to strengthen the transparency of EPA regulatory science. The proposed regulation provides that, for the science pivotal to its significant regulatory actions, EPA will ensure that the data and models underlying the science is publicly available in a manner sufficient for validation and analysis. In this notice, EPA solicits comment on this proposal and how it can best be implemented in light of existing law and prior statements of policy that have called for increasing public access to data and influential scientific information used to inform federal regulation. EPA has not previously implemented these policies and guidance in a robust and consistent manner. This proposal will help ensure that EPA is pursuing its mission of protecting public health and the environment in a manner that the public can trust and understand.

*C. What is the agency's authority for taking this action?*

The Agency proposes to take this action under authority of the statutes it administers, including provisions providing general authority to promulgate regulations necessary to carry out the Agency's functions under these statutes and provisions specifically addressing the Agency's conducting of and reliance on scientific activity to inform those functions, including Clean Air Act sections 103, 301(a), 42 U.S.C. 7403, 7601(a); Clean Water Act sections 104, 501, 33 U.S.C. 1254, 1361; Safe Drinking Water Act sections 1442, 1450(a)(1), 42 U.S.C. 300j-1, 300j-9(a)(1); Resource Conservation and Recovery Act sections 2002(a)(1), 7009, 42 U.S.C. 6912(a)(1), 6979; Comprehensive Environmental Response, Compensation, and Liability Act (as delegated to the Administrator via Executive Order 12580) sections 115, 311, 42 U.S.C. 9616, 9660; Emergency Planning and Community Right-To-Know Act section 328, 42 U.S.C. 11048;



ED_002751_00006736-00004

Federal Insecticide, Fungicide, and Rodenticide Act sections 25(a)(1), 136r(a), 7 U.S.C. 136r(a), 136w; and Toxic Substances Control Act, as amended, section 10, 15 U.S.C. 2609. This action is also consistent with requirements in the Administrative Procedure Act to ensure public participation in the rulemaking process. As noted in Section III below, EPA solicits comment on whether additional or alternative sources of authority are appropriate bases for this proposed regulation.

## II. Background

The best available science must serve as the foundation of EPA's regulatory actions.[1] Enhancing the transparency and validity of the scientific information relied upon by EPA strengthens the integrity of EPA's regulatory actions and its obligation to ensure the Agency is not arbitrary in its conclusions. By better informing the public, the Agency in enhancing the public's ability to understand and meaningfully participate in the regulatory process.[2] In applying the best available science to its regulatory decision-making, EPA must comply with federal transparency and data integrity laws, and must also ensure=that its decision-making is marked by independence, objectivity, transparency, clarity, and reproducibility. Although these standards are important in all scientific endeavors, they are of paramount importance when the government relies on science to inform its significant regulatory decisions that will affect the public. When EPA develops significant regulations using public resources, including regulations for which the public is likely to bear the cost of compliance, EPA should ensure that the data and models

[1] See Exec. Order No. 13563, 76 Fed. Reg. 3821 (Jan. 21, 2011). "Our regulatory system must protect public health, welfare, safety, and our environment while promoting economic growth, innovation, competitiveness, and job creation. It must be based on the best available science."

[2] See Memorandum for the Heads of Executive Department and Agencies on Scientific Integrity (Mar. 9, 2009). "If scientific and technological information is developed and used by the Federal Government, it should ordinarily be made available to the public. To the extent permitted by law, there should be transparency in the preparation, identification, and use of scientific and technological information in policymaking."



ED_002751_00006736-00005

underlying scientific studies that are pivotal to the regulatory action are available to the public. This proposed rule is designed to increase transparency in the preparation, identification, and use of science in policymaking.

This proposed rule is consistent with the principles underlying the Administrative Procedure Act and programmatic statutes that EPA administers to disclose to the public the bases for agency rules and to rationally execute and adequately explain agency actions.[3] This proposed rule is also consistent with Executive Orders 13777[4] and 13783,[5] and the focus on transparency in OMB's *Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility and Integrity of Information Disseminated by Federal Agencies*[6] (the Guidelines) and OMB *Memorandum 13-13: Open Data Policy – Managing Information as an Asset.*[7] It builds upon prior EPA actions[8] in response to government-wide data access and sharing policies, as well as the experience of other

---

[3] EPA has the authority to establish policies governing its reliance on science in the administration of its regulatory functions. Historically, EPA has not consistently observed the policies underlying this proposal, and courts have at times upheld EPA's use non-public data in support of its regulatory actions. *See Coalition of Battery Recyclers Ass'n v. EPA*, 604 F.3d 613, 623 (D.C. Cir. 2010); *American Trucking Ass'ns v. EPA*, 283 F.3d 355, 372 (D.C. Cir. 2002). EPA is proposing to exercise its discretionary authority to establish a policy that would preclude it from using such data in future regulatory actions.

[4] Exec. Order No. 13777, 82 Fed. Reg. 12285 (Mar. 1, 2017). Regulatory reform efforts shall attempt to identify "those regulations that rely in whole or in part on data, information, or methods that are not publicly available or that are insufficiently transparent to meet the standard for reproducibility."

[5] Exec. Order No. 13783, 82 Fed. Reg. 16093 (Mar. 31, 2017). "It is also the policy of the United States that necessary and appropriate environmental regulations comply with the law, are of greater benefit than cost, when permissible, achieve environmental improvements for the American people, and are developed through transparent processes that employ the best available peer-reviewed science and economics."

[6] February 22, 2002 (67 F.R 8453) *OMB's Guidelines Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information* (2002) https://www.federalregister.gov/documents/2002/02/22/R2-59/guidelines-for-ensuring-and-maximizing-the-quality-objectivity-utility-and-integrity-of-information.

[7] *Memorandum for the Heads of Executive Departments and Agencies on Open Data Policy—Managing Information as an Asset* (https://project-open-data.cio.gov/policy-memo/). "Specifically, this Memorandum requires agencies to collect or create information in a way that supports downstream information processing and dissemination activities. This includes using machine-readable and open formats, data standards, and common core and extensible metadata for all new information creation and collection efforts. It also includes agencies ensuring information stewardship through the use of open licenses and review of information for privacy, confidentiality, security, or other restrictions to release."

[8] Plan to Increase Access to Results of EPA-Funded Scientific Research; EPA Open Government Plan 4.0; Open Data Implementation Plan; EPA's Scientific Integrity Policy; Guidelines for Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information Disseminated by the Environmental Protection Agency; ;



ED_002751_00006736-00006

federal agencies in this space.[9] In particular, this proposal applies concepts and lessons learned from its ongoing implementation of the 2016 Plan to Increase Access to Results of EPA-Funded Scientific Research to significant regulatory decisions. The proposed rule takes into consideration the policies or recommendations of third party organizations who advocated for open science.[10] These policies are informed by the policies recently adopted by some major scientific journals,[11] spurred in some part by the "replication crisis." [12]

Today, EPA is proposing to establish a clear policy for the transparency of the scientific information used for significant regulations: specifically, the dose response data and models that underlie what we are calling "pivotal regulatory science." "Pivotal regulatory science" is the studies, models, and analyses that drive the magnitude of the benefit-cost calculation, the level of a standard, or point-of-departure from which a reference value is calculated. In other words, they are critical to the calculation of a final regulatory standard or level, or to the quantified costs, benefits, risks and other impacts on which a final regulation is based.

With this notice, EPA is soliciting public comment on a proposed regulation designed to provide a mechanism to increase access to dose response data and models underlying pivotal regulatory

---

[9] For example, see related policies from the National Science Foundation, National Institute of Science and Technology, the National Institutes of Health; and the US Census Bureau, which provides secure access to data from several agencies in an environment that protects against unauthorized disclosure (https://www.census.gov/fsrdc).

[10] These include policies and recommendations from: the Administrative Conference of the United States' Science in the Administrative Process Project; National Academies' reports on *Improving Access to and Confidentiality of Research Data*, *Expanding Access to Research Data*, and *Access to Research Data in the 21st Century*; the Health Effects Institute; Center for Open Science; members of the Risk Assessment Specialty Section of the Society of Toxicology, the Dose Response Section of the Society for Risk Analysis, and the International Society for Regulatory Toxicology and Pharmacology; and the Bipartisan Policy Center's Science for Policy Project.

[11] For example, see related policies from the *Proceedings of the National Academy of Sciences*, *PLOS ONE*, *Science*, and *Nature*.

[12] See: https://www.nature.com/articles/s41562-016-0021; http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.0020124; http://science.sciencemag.org/content/343/6168/229.long; https://www.economist.com/news/leaders/21588069-scientific-research-has-changed-world-now-it-needs-change-itself-how-science-goes-wrong.; http://stm.sciencemag.org/content/8/341/341ps12.full



ED_002751_00006736-00007

science in a manner consistent with statutory requirements for protection of privacy and confidentiality of research participants, protection of proprietary data and confidential business information, and other compelling interests. The proposal takes comment on how to ensure that, over time, more of the data and models underlying the science that informs regulatory decisions (over and above the dose response data and models underlying "pivotal regulatory science") is available to the public for validation[13] in a manner that honors legal and ethical obligations to reduce the risks of unauthorized disclosure and re-identification. As such this proposed regulation is designed to change agency culture and practices regarding data access so that the scientific justification for regulatory actions is truly available for validation and analysis. Regulatory determinations based on science should describe and document any assumptions and methods used, and should address variability and uncertainty. Where available and appropriate, EPA will use peer-reviewed information, standardized test methods, consistent data evaluation procedures, and good laboratory practices to ensure transparent, understandable, and reproducible scientific assessments. EPA's regulatory science should be consistent with the Office of Management and Budget's *Final Information Quality Bulletin for Peer Review*.[14] Robust peer review plays a critical role in independently validating key findings and ensuring that the quality of published information meets the standards of the scientific and technical community.

In addition, this proposed regulation is designed to increase transparency of the assumptions underlying dose response models. As a case in point, there is growing empirical evidence of non-

[13] EPA has not consistently followed previous EPA policy (e.g, EPA's Scientific Integrity Guidance, referenced above) that encouraged the use of non-proprietary data and models.
[14] https://www.whitehouse.gov/wp-content/uploads/2017/11/2005-M-05-03-Issuance-of-OMBs-Final-Information-Quality-Bulletin-for-Peer-Review-December-16-2004.pdf



ED_002751_00006736-00008

linearity in the concentration-response function for specific pollutants and health effects. The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies that explore: a broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models.

Across EPA programs, much of the science that informs regulatory actions is developed outside the Agency. It is the charge of regulators to ensure that key findings are valid and credible, as required by OMB's Guidelines[15] (which apply to "third party" information - e.g., non-government scientific research – if the agency use of that information provides the appearance of representing agency views). Using scientific information that can be independently validated will lead to better outcomes, and strengthen public confidence in the health and environmental protections underpinning EPA's regulatory actions.

EPA believes that concerns about access to confidential or private information can, in many cases, be addressed through the application of solutions commonly in use across some parts of

[15] February 22, 2002 (67 F.R 8453) *OMB's Guidelines Ensuring and Maximizing the Quality, Objectivity, Utility, and Integrity of Information* (2002) https://www.federalregister.gov/documents/2002/02/22/R2-59/guidelines-for-ensuring-and-maximizing-the-quality-objectivity-utility-and-integrity-of-information



ED_002751_00006736-00009

the Federal government.[16] Nothing in the proposed rule compels the disclosure of any confidential or private information in a manner that violates applicable legal and ethical protections. Other federal agencies have developed tools and methods to de-identify private information for a variety of disciplines.[17] The National Academies have noted that simple data masking, coding, and de-identification techniques have been developed over the last half century and that "Nothing in the past suggests that increasing access to research data without damage to privacy and confidentiality rights is beyond scientific reach."[18] More recently, both the National Academies and the Bipartisan Commission on Evidence Based Policy[19] have discussed the challenges and opportunities for facilitating to secure access to confidential data for non-government analysts.

Considering the breadth of dose response data and models used in the development of significant EPA regulations, the requirements for availability may differ. These mechanisms may range from deposition in public data repositories, consistent with requirements for many scientific journals,[20] to, for certain types of information, controlled access in federal research data centers that facilitate secondary research use by the public.[21] EPA should collaborate with other federal agencies to identify strategies to protect confidential and private information in any circumstance in which it is making information publicly available. These strategies should be cost-effective

---

[16] See examples from the U.S. Department of Health and Human Services, National Institute of Standards and Technology, U.S. Department of Education, and the U.S. Census Bureau.

[17] https://www.hhs.gov/hipaa/for-professionals/privacy/special-topics/de-identification/index.html.

[18] https://www.nap.edu/catalog/11434/expanding-access-to-research-data-reconciling-risks-and-opportunities.

[19] https://www.cep.gov/content/dam/cep/report/cep-final-report.pdf; https://www.nap.edu/catalog/24652/innovations-in-federal-statistics-combining-data-sources-while-protecting-privacy; https://www.nap.edu/catalog/24893/federal-statistics-multiple-data-sources-and-privacy-protection-next-steps.

[20] For example, see policies or recommendations of publishers Taylor & Francis, Elsevier, PLOS, and Springer Nature.

[21] For example: https://osp.od.nih.gov/scientific-sharing/requesting-access-to-controlled-access-data-maintained-in-nih-designated-data-repositories-e-g-dbgap/; https://www.census.gov/fsrdc.



ED_002751_00006736-00010

and may also include: requiring applications for access; restricting access to data for the purposes of replication, validation, and sensitivity evaluation; establishing physical controls on data storage; online training for researchers; and nondisclosure agreements.[22]

Implementation of this proposed rule will be consistent with the definition of "research data" in Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards, exemptions in P.L. 89-487, and other applicable federal laws.

This proposed regulation is intended to apply prospectively to final regulations that are determined to be "significant regulatory actions" pursuant to E.O. 12866. The Agency's offices should be guided by this policy to the maximum extent practicable during ongoing regulatory action, even where such research has already been generated, solicited, or obtained.

## III. Request for Comment

EPA solicits comment on all aspects of the proposed regulation and the bases articulated for it above. Specifically, EPA believes that it has identified appropriate sources of statutory authority for this proposed regulation in Section I(c) above, and solicits public comment on whether additional or alternative sources of authority are appropriate bases for this proposed regulation.

EPA further believes that a generally applicable regulatory provision of the type proposed here is the appropriate vehicle to establish and implement the policies articulated in Section II above, in the interests of consistency, predictability, and transparency across the functions that EPA performs.

EPA solicits comment on whether alternative or additional regulatory or other policy vehicles are appropriate to establish and implement these policies, and whether further regulatory or other

[22]These recommendations are consistent with those of Lutter and Zorn (2016). https://www.mercatus.org/system/files/Mercatus-Lutter-Public-Access-Data-v3.pdf.we re



ED_002751_00006736-00011

policy vehicles at the programmatic or statutory level would be appropriate as alternative or additional steps the agency may take to further the policies articulated in Section II above. EPA solicits comment on the effects of this proposed rule on individual EPA programs, including whether certain activities are appropriate to be excepted or if other requirements would affect implementation. EPA also seeks comments on which criteria the Agency should use to base any exceptions, including whether case-by-case exceptions may be appropriate. Although the proposed regulatory text would impose requirements specifically on final regulations determined to be "significant regulatory actions" under E.O. 12866, EPA solicits comment on whether and to what extent these requirements, or other provisions and policies, should apply to other stages of the rulemaking process, including proposed rules, as well as to other types of agency actions and promulgations, such as guidance. EPA also solicits comment on whether a narrower scope of coverage would be appropriate, such as only final regulations that are determined to be "major" under the Congressional Review Act, or "economically significant" under EO 12866. EPA also requests comment on whether certain categories of regulations should be excluded from coverage, such as those that merely reaffirm an existing standard, or some other category. For instance, we request comment on whether the provisions of the proposed rule should apply to individual party adjudications, enforcement activities, or permit proceedings when EPA determines that these provisions are practical and appropriate and that the actions are scientifically or technically novel or likely to have precedent-setting influence on future actions. EPA seeks comment on whether the Agency should apply the provisions of the proposed rule to these actions or to specific types of actions within these categories. The Agency also seeks comment on whether other agency actions, beyond significant



ED_002751_00006736-00012

final regulatory actions under EO 12866, should be included, such as site-specific permitting actions or non-binding regulatory determinations.

EPA solicits comment on the definitions of "*pivotal regulatory science*," and "*dose response data and models*" and how to implement such definitions.

EPA also solicits comment on how to incorporate stronger data and model access requirements into the terms and conditions of cooperative agreements and grants. EPA solicits comments on how it can build upon other federal agencies' policies regarding grantee and cooperator requirements for data access and data sharing. EPA also solicits suggestions for a platform that would enable the Agency to implement the provisions of this proposal related to increasing public access to EPA-funded data. EPA also seeks comment on methodologies and technologies designed to provide protected access to identifiable and sensitive data, such as individual health data, and on commenters experience with the use of such methodologies and technologies and their strengths and limitations. Similarly, EPA seeks comment on how to balance appropriate protection for copyrighted or confidential business information, including where protected by law, with requirements for increased transparency of pivotal regulatory science. EPA also requests comment on whether there are other compelling interests besides privacy, confidentiality, national and homeland security that may require special consideration when data is being released.

EPA solicits comment on implementation of the proposed regulation, including which parts of the Agency should be responsible for carrying out these requirements. EPA seeks comment on the effective date of a rule as well as on whether the Agency should seek to phase-in the requirements for certain significant regulatory actions or seek to prioritize specific actions. For regulatory programs, like the National Ambient Air Quality Standards program, in which future



ED_002751_00006736-00013

significant regulatory actions may be based on the administrative record from previous reviews - particularly where the governing statute requires repeated review on a fixed, date-certain cycle - EPA seeks comment on the manner in which this proposed rule should apply to that previous record. EPA also solicits comments on whether and how the proposed rule should apply to dose response data and models underlying pivotal regulatory science if those data and models were developed prior to the effective date. In addition, EPA seeks comment on how the prospective or retrospective application of the provisions for dose response data and models or pivotal regulatory science could inadvertently introduce bias regarding the timeliness and quality of the scientific information available. EPA seeks comment on how to address a circumstance in which EPA has a statutory requirement to make a determination for which scientific information publicly available in a manner sufficient for independent validation does not exist. EPA also seeks comment on any additional implementation challenges not discussed in this notice that commenters may be aware of as well as suggestions for addressing them.

The proposed rule includes a provision allowing the Administrator to exempt significant regulatory decisions on a case-by-case basis if he or she determines that compliance is impracticable because it is not feasible to ensure that all dose response data and models underlying pivotal regulatory science are publicly available in a fashion that is consistent with law, protects privacy and confidentiality, and is sensitive to national and homeland security, or in instances where OMB's Information Quality Bulletin for Peer Review provides for an exemption (Section IX). The agency requests comment on whether these exemptions are appropriate, and on whether there are other situations in which specific significant regulatory actions, or specific categories of significant regulatory actions should be exempted.



ED_002751_00006736-00014

EPA also requests comment on whether the disclosure requirements applicable to dose response data and models in the proposed rule should be expanded to cover other types of data and information, such as for example economic and environmental impact data and models that are designed to predict the costs, benefits, market impacts and/or environmental effects of specific regulatory interventions on complex economic or environmental systems.

## IV. Statutory and Executive Orders Reviews

### *A. Executive Order 12866: Regulatory Planning and Review and Executive Order 13563: Improving Regulation and Regulatory Review*

This action is a significant regulatory action that was submitted to the Office of Management and Budget (OMB) for review. Any changes made in response to OMB recommendations have been documented in the docket.

EPA believes the benefits of this proposed rule justify the costs. The benefits of EPA ensuring that dose response data and models underlying pivotal regulatory science are publicly available in a manner sufficient for independent validation are that it will improve the data and scientific quality of the Agency's actions and facilitate expanded data sharing and exploration of key data sets; this is consistent with the conclusions of the National Academies[23] This action should be implemented in a cost-effective way and is consistent with recent activities of the scientific community and other federal agencies, which will help to lower costs of implementation. The proposed rule directs EPA to make all reasonable efforts to explore methodologies, technologies, and institutional arrangements for making dose response models and data underlying pivotal regulatory science used in significant regulatory decisions available to the public in a manner sufficient for independent validation, consistent with law and protection of privacy,

[23] https://www.nap.edu/catalog/11434/expanding-access-to-research-data-reconciling-risks-and-opportunities.

confidentiality, and national and homeland security. However, it does not compel the Agency to make that information available where it concludes after all such reasonable efforts that doing so in way that complies with the law and appropriate protections is not possible.

By limiting the proposed rule to pivotal regulatory science for final significant regulatory actions pursuant to EO 12866, the proposed rule ensures that this standard for transparency affects a smaller subset of regulations which are economically significant, create inconsistency for other federal agencies, alter budgetary impacts, or raise novel legal or policy issues. One recent analysis found that: "Improvements in reproducibility can be thought of as increasing the net benefits of regulation because they would avoid situations in which costs or benefits are wrongly estimated to occur or in which regulatory costs are imposed without corresponding benefits. ..." They concluded that "an increase in existing net benefits from greater reproducibility, which, if it occurred, would cover the costs of obtaining the data and making the data available."[24]

*B. Executive Order 13771: Reducing Regulations and Controlling Regulatory Costs*

This action is not expected to be an Executive Order 13771 regulatory action because it relates to "agency organization, management or personnel."

*C. Paperwork Reduction Act (PRA)*

This action does not contain any information collection activities and therefore does not impose an information collection burden under the PRA.

*D. Regulatory Flexibility Act (RFA)*

I certify that this action will not have a significant economic impact on a substantial number of small entities under the RFA. This action will not impose any requirements on small entities.

[24] https://www.mercatus.org/system/files/Mercatus-Lutter-Public-Access-Data-v3.pdf.



ED_002751_00006736-00016

*E. Unfunded Mandates Reform Act (UMRA)*

This action does not contain any unfunded mandate as described in UMRA, 2 U.S.C. 1531–1538, and does not significantly or uniquely affect small governments. The action imposes no enforceable duty on any state, local or tribal governments or the private sector.

*F. Executive Order 13132: Federalism*

This action does not have federalism implications. It will not have substantial direct effects on the states, on the relationship between the national government and the states, or on the distribution of power and responsibilities among the various levels of government.

*G. Executive Order 13175: Consultation and Coordination with Indian Tribal Governments*

This action does not have tribal implications as specified in Executive Order 13175. Thus, Executive Order 13175 does not apply to this action.

*H. Executive Order 13045: Protection of Children from Environmental Health Risks and Safety Risks*

The EPA interprets Executive Order 13045 as applying only to those regulatory actions that concern environmental health or safety risks that the EPA has reason to believe may disproportionately affect children, per the definition of "covered regulatory action" in section 2-202 of the Executive Order. This action is not subject to Executive Order 13045 because it does not concern an environmental health risk or safety risk.

*I. Executive Order 13211: Actions Concerning Regulations That Significantly Affect Energy Supply, Distribution or Use*

This action is not a "significant energy action" because it is not likely to have a significant adverse effect on the supply, distribution or use of energy.



ED_002751_00006736-00017

*J. National Technology Transfer and Advancement Act (NTTAA)*

This rulemaking does not involve technical standards.

*K. Executive Order 12898: Federal Actions to Address Environmental Justice in Minority Populations and Low-Income Populations*

The EPA believes that this action is not subject to Executive Order 12898 (59 FR 7629, February 16, 1994) because it does not establish an environmental health or safety standard.



ED_002751_00006736-00018

**List of Subjects in 40 CFR Part 30**

Environmental protection, Administrative practice and procedure, Reporting and recordkeeping requirements.

Dated: APR 24 2018.

E. Scott Pruitt,

Administrator

For the reasons set forth in the preamble, EPA proposes to add 40 CFR part 30 as follows:

**PART 30—Transparency in Regulatory Decisionmaking**

1. Add part 30 to read as follows:

**PART 30—Transparency in Regulatory Decisionmaking**

Sec.


30.1 What is the purpose of this subpart?

30.2 What definitions apply to this subpart?

30.3 How do the provisions of this subpart apply?

30.4 What requirements apply to EPA's use of studies in taking final action?

30.5 What requirements apply to EPA's use of dose response data and models underlying pivotal regulatory science?

30.6 What additional requirements pertain to the use of dose response data and models underlying pivotal regulatory science?

30.7 What role does independent peer review play in this section?

30.8 How is EPA to account for cost under this subpart?

30.9 May the EPA Administrator grant exemptions to this subpart?

30.10 What other requirements apply under this subpart?




ED_002751_00006736-00020

Authority: Clean Air Act §§ 103, 301(a), 42 U.S.C. §§ 7403, 7601(a); Clean Water Act §§ 104, 501, 33 U.S.C. §§ 1254, 1361; Safe Drinking Water Act §§ 1442, 1450(a)(1), 42 U.S.C. §§ 300j-1, 300j-9(a)(1); Resource Conservation and Recovery Act §§ 2002(a)(1), 7009, 42 U.S.C. §§ 6912(a)(1), 6979; Comprehensive Environmental Response, Compensation, and Liability Act (as delegated to the Administrator via Executive Order 12580) §§ 115, 311, 42 U.S.C. §§ 9616, 9660; Emergency Planning and Community Right-To-Know Act § 328, 42 U.S.C. § 11048; Federal Insecticide, Fungicide, and Rodenticide Act §§ 25(a)(1), 136r(a), 7 U.S.C. §§ 136r(a), 136w; and Toxic Substances Control Act, as amended, § 10, 15 U.S.C. § 2609.

**§30.1 What is the purpose of this subpart?**

This subpart directs EPA to ensure that the regulatory science underlying its actions is publicly available in a manner sufficient for independent validation.

**§30.2 What definitions apply to this subpart?**

As used in this subpart, all terms not defined herein shall have the meaning given them in the Act or in subpart A; and the following terms shall have the specific meanings given them.

*Dose response data and models* means the data and models used to characterize the quantitative relationship between the amount of dose or exposure to a pollutant, contaminant, or substance and the magnitude of a predicted health or environmental impact. Such functions



ED_002751_00006736-00021

typically underlie pivotal regulatory science that drives the size of benefit-cost calculations, the level of a standard, and/or the points of departure from which reference values (reference doses or reference concentrations) are calculated.

*Pivotal regulatory science* means the specific scientific studies or analyses that drive the requirements and/or quantitative analysis of EPA final significant regulatory decisions.

*Regulatory decisions* mean final regulations determined to be "significant regulatory actions" by the Office of Management and Budget pursuant to Executive Order 12866.

*Regulatory science* means scientific information, including assessments, models, criteria documents, and regulatory impact analyses, that provide the basis for EPA final significant regulatory decisions.

*Research data* means "research data" as that term is defined in Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards.

**§30.3 How do the provisions of this subpart apply?**

The provisions of this subpart apply to *dose response data and models* underlying *pivotal regulatory science* that are used to justify significant *regulatory decisions* regardless of the source of funding or identity of the party conducting the regulatory science. The provisions of



ED_002751_00006736-00022

this section do not apply to physical objects (like laboratory samples), drafts, and preliminary analyses. Except where explicitly stated otherwise, the provisions of this subpart do not apply to any other type of agency action, including individual party adjudications, enforcement activities, or permit proceedings.

**§30.4 What requirements apply to EPA's use of studies in taking final action?**

EPA shall clearly identify all studies (or other regulatory science) relied upon when it takes any final agency action. EPA should make all such studies available to the public to the extent practicable.

**§30.5 What requirements apply to EPA's use of dose response data and models underlying pivotal regulatory science?**

When promulgating significant regulatory actions, the Agency shall ensure that *dose response data and models* underlying *pivotal regulatory science* are publicly available in a manner sufficient for independent validation. Where the Agency is making data or models publicly available, it shall do so in a fashion that is consistent with law, protects privacy, confidentiality, confidential business information, and is sensitive to national and homeland security. Information is considered "publicly available in a manner sufficient for independent validation" when it includes the information necessary for the public to understand, assess, and replicate findings. This may include, for example:



ED_002751_00006736-00023

(a) Data (where necessary, data would be made available subject to access and use restrictions).

(b) Associated protocols necessary to understand, assess, and extend conclusions;

(c) Computer codes and models involved in the creation and analysis of such information;

(d) Recorded factual materials; and

(e) Detailed descriptions of how to access and use such information.

The provisions of this section apply to dose response data and models underlying pivotal regulatory science regardless of who funded or conducted the underlying data, models, or other regulatory science. The agency shall make all reasonable efforts to explore methodologies, technologies, and institutional arrangements for making such data available before it concludes that doing so in a manner consistent with law and protection of privacy, confidentiality, national and homeland security is not possible. Where data is controlled by third parties, EPA shall work with those parties to endeavor to make the data available in a manner that complies with this section.

**§30.6 What additional requirements pertain to the use of dose response data and models underlying pivotal regulatory science?**

EPA shall describe and document any assumptions and methods used, and should describe variability and uncertainty. EPA shall evaluate the appropriateness of using default



ED_002751_00006736-00024

assumptions, including assumptions of a linear, no-threshold dose response, on a case-by-case basis. EPA shall clearly explain the scientific basis for each model assumption used and present analyses showing the sensitivity of the modeled results to alternative assumptions. When available, EPA shall give explicit consideration to high quality studies that explore: a broad class of parametric dose-response or concentration-response models; a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the dose or exposure range; and models that investigate factors that might account for spatial heterogeneity.

**§30.7 What role does independent peer review in this section?**

EPA shall conduct independent peer review on all *pivotal regulatory science* used to justify *regulatory decisions,* consistent with the requirements of the OMB Final Information Quality Bulletin for Peer Review (70 FR 2664) and the exemptions described therein.

Because transparency in regulatory science includes addressing issues associated with assumptions used in models, EPA shall ask peer reviewers to articulate the strengths and weaknesses of EPA's justification for the assumptions applied and the implications of those assumptions for the results.

**§30.8 How is EPA to account for cost under this subpart?**



ED_002751_00006736-00025

EPA shall implement the provisions of this subpart in a manner that minimizes costs.

**§30.9 May the EPA Administrator grant exemptions to this subpart?**

Yes. The Administrator may grant an exemption to this subpart on a case-by-case basis if he or she determines that compliance is impracticable because:

(a) It is not feasible to ensure that all dose response data and models underlying pivotal regulatory science is publicly available in a manner sufficient for independent validation, in a fashion that is consistent with law, protects privacy, confidentiality, confidential business information, and is sensitive to national and homeland security; or

(b) It is not feasible to conduct independent peer review on all pivotal regulatory science used to justify regulatory decisions for reasons outlined in OMB Final Information Quality Bulletin for Peer Review (70 FR 2664), Section IX.

**§30.10 What other requirements apply under this subpart?**

EPA shall implement the provisions of this section consistent with the definition of "research data" in Uniform Administrative Requirements, Cost Principles, and Audit Requirements for Federal Awards, exemptions in P.L. 89-487, and other applicable federal laws.



ED_002751_00006736-00026

Where appropriate, data sharing agreements and state-of-the-art data-masking techniques may be employed to facilitate access to information.



ED_002751_00006736-00027

Message

**From:** Woods, Clint [woods.clint@epa.gov]
**Sent:** 4/20/2018 6:20:52 PM
**To:** Bowman, Liz [Bowman.Liz@epa.gov]; Bolen, Brittany [bolen.brittany@epa.gov]; Gordon, Stephen [gordon.stephen@epa.gov]; Konkus, John [konkus.john@epa.gov]; Letendre, Daisy [letendre.daisy@epa.gov]; Schwab, Justin [Schwab.Justin@epa.gov]
**Subject:** Transparency/Data Access Statements of Support

Happy to work on some talking points for a release to accompany Tuesday's announcement.

We should have 2-3 sentence statements of support from:

- Jason Scott Johnston, PhD/JD, Director, Olin Law and Economics Program, University of Virginia School of Law
- Edward J. Calabrese, PhD, Professor, Environmental Health Sciences, University of Massachusetts
- Louis Anthony (Tony) Cox, Jr., PhD, President, Cox Associates, Member, National Academy of Engineering, Editor-in-Chief, *Risk Analysis*
- Bruno Pigott, Commissioner, Indiana Department of Environmental Management
- George Wolff, PhD, Former Chair of EPA's Clean Air Scientific Advisory Committee (1993 – 1996)

A few examples:

"IDEM supports transparency in rulemaking", says Bruno Pigott, Commissioner of the Indiana Department of Environmental Management (IDEM). "Good, sound science leads to better regulations."

"The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process," stated Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts

"I believe that transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science," said Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the journal *Risk Analysis*. "Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

Message

**From:** Woods, Clint [woods.clint@epa.gov]
**Sent:** 11/21/2018 12:49:05 PM
**To:** Konkus, John [konkus.john@epa.gov]
**Subject:** Re: Ed Calabrese

**Ex. 5 Deliberative Process (DP)**

On Nov 21, 2018, at 7:46 AM, Konkus, John <konkus.john@epa.gov> wrote:

Please edit this as you see fit: **Ex. 5 Deliberative Process (DP)**

**Ex. 5 Deliberative Process (DP)**

John Konkus
Environmental Protection Agency
Deputy Associate Administrator
Office of Public Affairs

On Nov 21, 2018, at 7:35 AM, Woods, Clint <woods.clint@epa.gov> wrote:

Ms. Rust,

Thanks so much for your email - Our press team will be in touch.

Clint

On Nov 20, 2018, at 12:33 PM, Rust, Susanne <susanne.rust@latimes.com> wrote:

Dear Mr Woods,

I'm a reporter at the Los Angeles Times working on a story about hormesis, Ed Calabrese, LNT and the EPA's proposed new rule on transparency in science.
I came across some emails you exchanged with Dr. Calabrese this spring about LNT. According to the chronology, you sought Calabrese's advice on what to incorporate into the rule, you spoke, and he also provided you with language to use, which was then incorporated into the rule - word-for-word.
I wonder if you could answer some questions about this exchange for me?

1) Who suggested you contact Calabrese?
2) What other toxicologists/scientists did you consult with?
3) In one of your emails, you mentioned that you and Calabrese had known one another years ago. Can you tell me how?

Thanks for your time. Feel free to call me at: 650-804-6790.

Susanne Rust

Reporter, The Los Angeles Times

Ex. 6 Personal Privacy (PP)

Message

**From**: Block, Molly [block.molly@epa.gov]
**Sent**: 4/24/2018 7:54:05 PM
**To**: Tollefson, Jeff [J.Tollefson@us.nature.com]; Press [Press@epa.gov]
**Subject**: RE: query from Nature
**Attachments**: Strengthening Transparency in Regulatory Science 04-24-2018.pdf

See attached.

---

**From:** Tollefson, Jeff [mailto:J.Tollefson@us.nature.com]
**Sent:** Tuesday, April 24, 2018 3:53 PM
**To:** Press <Press@epa.gov>
**Subject:** query from Nature

Hello,
Can we get a copy of the proposed rule? Or the order that was signed? I don't see anything on the federal register or anything in the news release below. We're running a story today, so the deadline is this afternoon.

Many thanks,
Jeff

==========

nature
Jeff Tollefson, US Correspondent
j.tollefson@us.nature.com
One New York Plaza, Suite 4500, New York, NY 10004-1562
Ex. 6 Personal Privacy (PP)
www.nature.com/news

# News Releases

CONTACT US

SHARE

# News Releases from Headquarters›Office of the Administrator (AO)

# EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

04/24/2018

Contact Information:
EPA Press Office (press@epa.gov)

**WASHINGTON** (April 24, 2018) – Today, U.S. Environmental Protection Agency (EPA) Administrator Scott Pruitt signed a proposed rule to strengthen the science used in regulations issued by EPA. The rule will ensure that the regulatory science underlying Agency actions is fully transparent, and that underlying scientific information is publicly available in a manner sufficient for independent validation.

"The era of secret science at EPA is coming to an end," **said EPA Administrator Scott Pruitt.** "The ability to test, authenticate, and reproduce scientific findings is vital for the integrity of rulemaking process. Americans deserve to assess the legitimacy of the science underpinning EPA decisions that may impact their lives."

This proposed rule is in line with the scientific community's moves toward increased data sharing to address the "replication crisis"—a growing recognition that a significant proportion of published research may not be reproducible. The proposal is consistent with data access requirements for major scientific journals like *Science*, *Nature*, and *Proceedings of the National Academy of Sciences* as well as recommendations from the Bipartisan Policy Center's Science for Policy Project and the Administrative Conference of the United States' Science in the Administrative Process Project.

The proposed rule builds upon President Trump's executive orders on regulatory reform and energy independence:

- **Executive Order 13777**, issued in March 2017, provides that regulatory reform efforts shall attempt to identify "those regulations that rely in whole or in part on data, information, or methods that are not publicly available or that are insufficiently transparent to meet the standard of reproducibility."
- **Executive Order 13783**, also issued in March 2017, provides that "It is the policy of the United States that necessary and appropriate environmental regulations comply with the law, are of greater benefit than cost, when permissible, achieve environmental improvements for the American people, and are developed through transparent processes that employ the best available peer-reviewed science and economics."

**Chairman Lamar Smith (R-TX):** "Administrator Pruitt's announcement ensures that data will be secret no more. For too long, the EPA has issued rules and regulations based on data that has been withheld from the American people. It's likely that in the past, the data did not justify all regulations. Today, Administrator Pruitt rightfully is changing business as usual and putting a stop to hidden agendas."

**Senator Mike Rounds (R-SD):** "Sound, reliable science is vital to helping us make important policy decisions that impact the health of American families and their livelihoods. Inserting new levels of transparency in the EPA rulemaking process will help make the agency more accountable to the American people and help everyone understand the impact of EPA's decisions. Today's directive is a significant step toward making sure these decisions are not made behind closed doors with information accessible only to those writing the regulations, but rather in the full view of those who will be affected."

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process."
**Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the Journal *Risk Analysis*:** "I believe that transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science. Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."
**Dr. Jason Scott Johnston, Director, Olin Law and Economics Program, University of Virginia School of Law:** "EPA's proposed rule, Strengthening Transparency in Regulatory Science, is badly needed "Best practice among peer-edited scientific journals is to require that data and statistical routines used in published papers be posted online and/or made publicly available. To apply the same standards to research that EPA says justify regulations affecting billions of dollars in economic activity and millions of human lives is essential for those regulations to truly be scientifically based."
**Bruno Pigott, Commissioner of the Indiana Department of Environmental Management (IDEM)**: "IDEM supports transparency in rulemaking. Good, sound science leads to better regulations."
**Dr. George Wolff, Principal Scientist, Air Improvement Resource, Inc., and former Chairman of EPA's Clean Air Scientific Advisory Committee (1992 – 1996):** "In the development of regulations based on environmental studies, numerous subjective assumptions and choices must be made regarding the selection of data and models that have a profound impact on the strength of any statistical associations and even whether the associations are positive or negative. The appropriateness of the assumptions and choices are not adequately evaluated in the standard peer review process. That is why it is essential that the data and models be placed in the public domain for a more rigorous evaluation by qualified experts. The proposed regulation, Strengthening Transparency in Regulatory Science, will provide an opportunity for such evaluations."

DISCLAIMER: This e-mail is confidential and should not be used by anyone who is not the original intended recipient. If you have received this e-mail in error please inform the sender and delete it from your mailbox or any other storage mechanism. Nature America, Inc. does not accept liability for any statements made which are clearly the sender's own and not expressly made on behalf of Nature America, Inc. or one of their agents.
Please note that neither Nature America, Inc. or any of its agents accept any responsibility for viruses that may be contained in this e-mail or its attachments and it is your responsibility to scan the e-mail and attachments (if any).

Message

**From**: Block, Molly [block.molly@epa.gov]
**Sent**: 7/16/2018 9:04:38 PM
**To**: Robinson Meyer [rob@theatlantic.com]
**CC**: Daguillard, Robert [Daguillard.Robert@epa.gov]; Press [Press@epa.gov]
**Subject**: RE: Press request from The Atlantic

Rob –

EPA is committed to public participation and transparency in the rulemaking process. On July 17, EPA is hosting a public hearing on the proposed rule, "Strengthening Transparency in Regulatory Science" in Washington, DC. The public comment period for the rule closes on August 16, 2018. The hearing will provide the public with an opportunity to present oral comments regarding EPA's proposed regulation. This proposed regulation is intended to strengthen the transparency of EPA regulatory science. EPA will consider all submitted comments—both those given orally at the hearing and those submitted in writing to the docket—as it moves forward in the rulemaking process.

**BACKGROUND:**
**On science transparency …**

- The proposed rule is in line with the scientific community's moves toward increased data sharing to address the "replication crisis," in which a significant proportion of published research may be false or not reproducible. Examples of the current data access provisions for authors publishing in major scientific journals:
  - *Science*: "All data used in the analysis must be available to any researcher for purposes of reproducing or extending the analysis."
  - *Nature*: "This policy builds upon our long-standing policy on data availability, which requires that authors make materials, data, code, and associated protocols promptly available to readers without undue qualifications. The preferred way to share large data sets is via public repositories."
  - *Proceedings of the National Academy of Sciences*: "To allow others to replicate and build on work published in PNAS, authors must make materials, data, and associated protocols, including code and scripts, available to readers."

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process."

**Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the Journal *Risk Analysis*:** "I believe that transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science. Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."

**Dr. Jason Scott Johnston, Director, Olin Law and Economics Program, University of Virginia School of Law:** "EPA's proposed rule, Strengthening Transparency in Regulatory Science, is badly needed. "Best practice" among peer-edited scientific journals is to require that data and statistical routines used in published papers be posted online and/or made publicly available. To apply the same standards to research that EPA says justify regulations affecting billions of dollars in economic activity and millions of human lives is essential for those regulations to truly be scientifically based."

**Dr. George Wolff, Principal Scientist, Air Improvement Resource, Inc., and former Chairman of EPA's Clean Air Scientific Advisory Committee (1992 – 1996):** "In the development of regulations based on environmental studies, numerous subjective assumptions and choices must be made regarding the selection of data and models that have a profound impact on the strength of any statistical associations and even whether the associations are positive or negative. The appropriateness of the assumptions and choices are not adequately evaluated in the standard peer review process. That is why it is essential that the data and models be placed in the public domain for a more rigorous evaluation by qualified experts. The proposed regulation, Strengthening Transparency in Regulatory Science, will provide an opportunity for such evaluations."

**From:** Robinson Meyer [mailto:rob@theatlantic.com]
**Sent:** Monday, July 16, 2018 4:29 PM
**To:** Daguillard, Robert <Daguillard.Robert@epa.gov>
**Subject:** Press request from The Atlantic

Hey Robert,

I'm a reporter at The Atlantic, where I cover the environment. I'm writing about the hearing scheduled Tuesday for the EPA's scientific transparency rule. I'm writing with two questions:

1. Does Administrator Wheeler plan to announce any substantive changes to the draft version of the scientific transparency rule at tomorrow's hearing? (I am happy to respect an embargo until the start of the event.)

2. A wide number of scientific or research institutions—including the journals Nature and Science, as well as the American Geophysical Union and Harvard University—have opposed the rule, declaring it far too strict to promote scientific transparency. Does the administrator or the agency have any comment on this wide condemnation (given that these are largely apolitical organizations)?

Many thanks. We can email or give me a call at Ex. 6 Personal Privacy (PP)

Rob

--
::::::

Robinson Meyer
Staff Writer, The Atlantic
phone // Ex. 6 Personal Privacy (PP)
skype // yayitsrob

Message

**From:** Abboud, Michael [abboud.michael@epa.gov]
**Sent:** 10/3/2018 11:34:36 PM
**To:** Beach, Christopher [beach.christopher@epa.gov]; Konkus, John [konkus.john@epa.gov]; Hewitt, James [hewitt.james@epa.gov]; Block, Molly [block.molly@epa.gov]
**Subject:** Fwd: 6 NEWS

Sent from my iPhone

Begin forwarded message:

**From:** Thomas Darling <TDarling@wlns.com>
**Date:** October 3, 2018 at 7:04:21 PM EDT
**To:** "Abboud, Michael" <abboud.michael@epa.gov>
**Subject: Re: 6 NEWS**

Mr. Abboud,

Thank you for taking the time to talk with me this evening. Clarifying widespread misinformation is one of the essential functions of journalism, especially when that misinformation comes from an otherwise-trustworthy journalistic source. The information you shared with me will be essential as I work to clarify the issue for my audience.

Thanks again,
Tom Darling

Producer

WLNS 6 News

---

**From:** Abboud, Michael <abboud.michael@epa.gov>
**Sent:** Wednesday, October 3, 2018 6:00 PM
**To:** Thomas Darling
**Subject:** RE: 6 NEWS

https://www.epa.gov/newsreleases/epa-administrator-pruitt-proposes-rule-strengthen-science-used-epa-regulations

---

**From:** Thomas Darling [mailto:TDarling@wlns.com]
**Sent:** Wednesday, October 3, 2018 5:52 PM

**To:** Abboud, Michael <abboud.michael@epa.gov>
**Subject:** Re: 6 NEWS

I can be reached at Ex. 6 Personal Privacy (PP)

---

**From:** Abboud, Michael <abboud.michael@epa.gov>
**Sent:** Wednesday, October 3, 2018 5:51 PM
**To:** Thomas Darling
**Subject:** RE: 6 NEWS

Tom, what's your phone number so I can explain this?

---

**From:** Singer, Joshua
**Sent:** Wednesday, October 3, 2018 5:50 PM
**To:** Abboud, Michael <abboud.michael@epa.gov>; Press <Press@epa.gov>
**Cc:** Rowan, Anne <rowan.anne@epa.gov>; Kelley, Jeff <kelley.jeff@epa.gov>; regionalpress <regionalpress@epa.gov>
**Subject:** FW: 6 NEWS

Michael,

Please see the follow-up email from Tom Darling at the Lansing TV station and let me know if you need assistance with responding. Thank you.

Josh Singer

U.S. EPA, Region 5

phone: 312-353-5069

singer.joshua@epa.gov

**From:** Thomas Darling [mailto:TDarling@wlns.com]
**Sent:** Wednesday, October 03, 2018 4:48 PM
**To:** Singer, Joshua <Singer.Joshua@epa.gov>
**Subject:** Re: 6 NEWS

Mr. Singer,

Thank you for this information. It is abundantly clear that the EPA is not planning changes to the linear no-threshold model of radiation exposure regulation, and I will make sure my viewers know that.

That said, I was hoping to find out what the EPA is actually doing. If you have any information on the actual proposed rule in question, it would be very helpful as I try to provide context for my viewers.

The corrected AP article also mentions that an April press release included comments from UMass toxicologist Edward Calabrese, the expert who holds that exposure to harmful chemicals and radiation can produce positive health results. I feel this is where some of the confusion came from, so if you could explain his contribution to the actual proposed rule change, that would also be of great interest.

Thank you for your help.

-Tom Darling

Producer

WLNS 6 News

---

**From:** Singer, Joshua <Singer.Joshua@epa.gov>
**Sent:** Wednesday, October 3, 2018 5:41 PM

**To:** Thomas Darling
**Subject:** RE: 6 NEWS

Tom,

Please attribute the information below to U.S. EPA. If this information does not answer your questions or you have more questions, please let me know. Thank you.

**The central point of their story has changed to reflect that critics of an unrelated proposed rule are the ones alleging that it would change radiation guidelines, not EPA.**

**EPA's policy has not – and is not expected to be – changed: "The proposed regulation doesn't talk about radiation or any particular chemicals. EPA's policy is to continue to use the linear-no-threshold model for population-level radiation protection purposes which would not – under the proposed regulation that has not been finalized – trigger any change in that policy."**

**Please see Associated Press Issues Correction to False Reporting: http://createsend.com/t/d-7B1B1A763AA87F9B2540EF23F30FEDED**

---

**From:** Thomas Darling [mailto:TDarling@wlns.com]
**Sent:** Wednesday, October 03, 2018 4:34 PM
**To:** Singer, Joshua <Singer.Joshua@epa.gov>
**Subject:** 6 NEWS

This is my correct email address.

-Tom Darling

Producer

WLNS 6 News

Message

**From**: Nath, David [David.Nath@FOXNEWS.COM]
**Sent**: 10/3/2018 8:04:00 PM
**To**: Konkus, John [konkus.john@epa.gov]; Conway, Maureen [maureen.conway@FOXNEWS.COM]
**CC**: Press [Press@epa.gov]
**Subject**: RE: Media Request on radiation regulations hearing

Thanks so much for your quick reply! I did see the corrected version, but the corrections seemed to be limited to the attribution of the "a little radiation" line. Seems they're sticking by the assertion that the original April release outlining the proposed change specifically referenced radiation levels via Dr. Calabrese's statement.

I am at Ex. 6 Personal Privacy (PP) - would love to discuss further.

---

**From:** Konkus, John [mailto:konkus.john@epa.gov]
**Sent:** Wednesday, October 3, 2018 3:54 PM
**To:** Nath, David <David.Nath@FOXNEWS.COM>; Conway, Maureen <maureen.conway@FOXNEWS.COM>
**Cc:** Press <Press@epa.gov>
**Subject:** RE: Media Request on radiation regulations hearing

What's your phone number?

AP ran a correction to their story: Associated Press Issues Correction to False Reporting: http://createsend.com/t/d-7B1B1A763AA87F9B2540EF23F30FEDED

The proposed regulation doesn't talk about radiation or any particular chemicals. EPA's policy is to continue to use the linear-no-threshold model for population-level radiation protection purposes which would not – under the proposed regulation that has not been finalized – trigger any change in that policy.

---

**From:** Nath, David [mailto:David.Nath@FOXNEWS.COM]
**Sent:** Wednesday, October 3, 2018 3:49 PM
**To:** Conway, Maureen <maureen.conway@FOXNEWS.COM>; Konkus, John <konkus.john@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** RE: Media Request on radiation regulations hearing

Hi John – according to AP, there was a Congressional hearing scheduled for today on the new proposal, with Edward Calabrese as the lead witness, but it was cancelled. We're still extremely interested in this story – it has a broad impact that will effect a lot of our viewers. Would it be possible to speak with someone? We're more interested in the science than the politics.

---

**From:** Conway, Maureen
**Sent:** Wednesday, October 3, 2018 3:42 PM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** RE: Media Request on radiation regulations hearing

Hi John

I forwarded your question to David Nath.. It is a story he is working on and I'm sure he can be more clear than I have been.
Expect to hear from him shortly
And thank you for getting back to me so quickly.

***Maureen Conway***
**Producer**
**Fox News Edge**
212-301-3586

---

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Wednesday, October 3, 2018 3:38 PM
**To:** Conway, Maureen <maureen.conway@FOXNEWS.COM>
**Cc:** Press <Press@epa.gov>
**Subject:** FW: Media Request on radiation regulations hearing

Maureen: What radiation regulation hearings are you referring to?

---

**From:** Conway, Maureen [mailto]
**Sent:** Wednesday, October 03, 2018 3:13 PM
**To:** Lynn, Tricia <lynn.tricia@epa.gov>
**Subject:** Media Request on radiation regulations hearing

Hi Lynn

My name is Maureen Conway. I'm the Health/Medical Producer for the Fox News affiliate news-sharing service. We are considering doing a package on the impact of the radiation regulation hearings tomorrow and we were wondering if anyone from the FDA may be available to comment on it tomorrow morning.

We have studios on Capitol Street in Washington, or if a spokesperson is available in New York they are more then welcome to come here for a visit at 1211 Avenue of the Americas between 47th and 48th Streets and we'll have them in and out in less than a half hour.

Please let me know if anything might be available.

Thank you for your time.

***Maureen Conway***
**Producer**
**Fox News Edge**
212-301-3586

This message and its attachments may contain legally privileged or confidential information. It is intended solely for the named addressee. If you are not the addressee indicated in this message (or responsible for delivery of the message to the addressee), you may not copy or deliver this message or its attachments to anyone. Rather, you should permanently delete this message and its attachments and kindly notify the sender by reply e-mail. Any content of this message and its attachments that does not relate to the official business of Fox News or Fox Business must not be taken to have been sent or endorsed by either of them. No representation is made that this email or its attachments are without defect.

Message

**From**: Jones, Enesta [Jones.Enesta@epa.gov]
**Sent**: 9/13/2018 9:45:49 PM
**To**: Press [Press@epa.gov]
**Subject**: FOR REVIEW: AP (Ellen Knickmeyer) RE: LNT standards vs. threshold, hermetic standards (9/17)

**Here's a revamped response, for your review. ORD reviewed and provided edits to the first graph.**

# Ex. 5 Deliberative Process (DP)

**From:** "Lynn, Tricia" <lynn.tricia@epa.gov>
**Date:** September 13, 2018 at 3:36:17 PM EDT

**To:** Press <Press@epa.gov>
**Subject: FOR REVIEW: AP (Ellen Knickmeyer) RE: LNT standards vs. threshold, hermetic standards (9/17)**

Reporter is asking about LNT standards vs. threshold, hermetic standards for radiation exposure. Ellen Knickmeyer, AP.

**Suggested Response:**

# Ex. 5 Deliberative Process (DP)

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, September 13, 2018 10:33 AM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Cc:** Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hello – wanted to also ask, is this still EPA policy?
https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
"Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."

"Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."

Best,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>
**Cc:** 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From**: Block, Molly [block.molly@epa.gov]
**Sent**: 10/3/2018 4:30:14 PM
**To**: Marsh, Rene [Rene.Marsh@cnn.com]; Konkus, John [konkus.john@epa.gov]; Hewitt, James [hewitt.james@epa.gov]; Press [Press@epa.gov]
**Subject**: RE: CNN

Please see Associated Press Issues Correction to False Reporting: http://createsend.com/t/d-7B1B1A763AA87F9B2540EF23F30FEDED

If you're still confused, we'd be happy to chat. The central point of their story has changed to reflect that critics of an unrelated proposed rule are the ones alleging that it would change radiation guidelines, not EPA.

EPA's policy has not – and is not expected to – changed: "The proposed regulation doesn't talk about radiation or any particular chemicals. EPA's policy is to continue to use the linear-no-threshold model for population-level radiation protection purposes which would not – under the proposed regulation that has not been finalized – trigger any change in that policy."

---

**From:** Marsh, Rene [mailto:Rene.Marsh@cnn.com]
**Sent:** Wednesday, October 3, 2018 12:23 PM
**To:** Konkus, John <konkus.john@epa.gov>; Hewitt, James <hewitt.james@epa.gov>; Press <Press@epa.gov>
**Subject:** Re: CNN

Morning all,

I see the AP posted that they are correcting an erroneous headline but maintains the central point of the story remains. " The EPA is pursuing rule changes that experts say would weaken the way radiation exposure is regulated, turning to scientific outliers who argue that a bit of radiation damage is actually good for you — like a little bit of sunlight."

Seems like their story overall remains the same.

---

**From:** "Konkus, John" <konkus.john@epa.gov>
**Date:** Tuesday, October 2, 2018 at 4:56 PM
**To:** "Marsh, Rene" <Rene.Marsh@cnn.com>, "Hewitt, James" <hewitt.james@epa.gov>, Press <Press@epa.gov>
**Subject:** RE: CNN

We have asked the AP to correct their as there is no "radiation regulation" as they put it, and we told them that on-the-record two weeks ago. The regulation the AP reporter asked about, Strengthening Transparency in Science, doesn't even mention the word "radiation."

---

**From:** Marsh, Rene [mailto:Rene.Marsh@cnn.com]
**Sent:** Tuesday, October 2, 2018 4:53 PM
**To:** Hewitt, James <hewitt.james@epa.gov>; Konkus, John <konkus.john@epa.gov>; Press <Press@epa.gov>
**Subject:** CNN

**Hello all,**

Some of here at CNN are not getting your press releases via email. Is there a mailing list that I may not be on? Could you add me to your list?

We see the below report that references an EPA press release that we did not receive regarding radiation.

WASHINGTON (AP) — The Trump administration is quietly moving to weaken U.S. radiation regulations, turning to scientific outliers who argue that a bit of radiation damage is actually good for you — like a little bit of sunlight.

The government's current, decades-old guidance says that any exposure to harmful radiation is a cancer risk. And critics say the proposed change could lead to higher levels of exposure for workers at nuclear installations and oil and gas drilling sites, medical workers doing X-rays and CT scans, people living next to Superfund sites and any members of the public who one day might find themselves exposed to a radiation release.

The Trump administration already has targeted a range of other regulations on toxins and pollutants, including coal power plant emissions and car exhaust, that it sees as costly and burdensome for businesses. Supporters of the EPA's new radiation guidance argue the government's current no-tolerance rule for radiation damage forces unnecessary spending for handling exposure in accidents, at nuclear plants, in medical centers and at other sites.

"This would have a positive effect on human health as well as save billions and billions and billions of dollars," Edward Calabrese, a toxicologist at the University of Massachusetts, said in 2016. He was to be the lead witness at a congressional hearing Wednesday on EPA's push for what it calls transparency in science.

The proposed rule would require regulators to consider "various threshold models across the exposure range" when it comes to dangerous substances.

While it does not specify that it's addressing radiation and chemicals, an EPA news release on the rule quotes Calabrese as saying it would: "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process."

The comment period for the science regulation has ended and the agency is currently reviewing the comments. There's no specific date for final action by the administration. The EPA declined to make an official with its radiation-protection program available.

Radiation is everywhere, from potassium in bananas to the microwaves popping our popcorn. Most of it is benign. But what's of concern is the higher-energy, shorter-wave radiation, like X-rays, that can penetrate and disrupt living cells, sometimes causing cancer.

As recently as this March, the EPA's online guidelines for radiation effects advised: "Current science suggests there is some cancer risk from any exposure to radiation."

"Even exposures below 100 millisieverts" — an amount roughly equivalent to 25 chest X-rays or about 14 CT chest scans — "slightly increase the risk of getting cancer in the future," the agency's guidance said.

But that online guidance — separate from the rule-change proposal — was edited in July to add a section emphasizing the low individual odds of cancer: "According to radiation safety experts, radiation exposures of ...100 millisieverts usually result in no harmful health effects, because radiation below these levels is a minor contributor to our overall cancer risk," the revised policy says.

Calabrese and his supporters argue that smaller exposures of cell-damaging radiation and other carcinogens can serve as stressors that activate the body's repair mechanisms and can make people healthier. They compare it to physical exercise or sunlight.

Mainstream scientific consensus on radiation is based on deceptive science, says Calabrese, who argued in a 2014 essay for "righting the past deceptions and correcting the ongoing errors in environmental regulation."

EPA spokesman John Konkus said in an email that the proposed rule change is about "increasing transparency on assumptions" about how the body responds to different doses of dangerous substances and that the agency "acknowledges uncertainty regarding health effects at low doses" and supports more research on that.

The radiation regulation is supported by Steven Milloy, a Trump transition team member for the EPA who is known for challenging widely accepted ideas about manmade climate change and the health risks of tobacco. He has been promoting Calabrese's theory of healthy radiation on his blog.

But Jan Beyea, a physicist whose work includes research with the National Academies of Science on the 2011 Fukushima nuclear power plant accident, said the EPA science proposal represents voices "generally dismissed by the great bulk of scientists."

The EPA proposal would lead to "increases in chemical and radiation exposures in the workplace, home and outdoor environment, including the vicinity of Superfund sites," Beyea wrote.

At the level the EPA website talks about, any one person's risk of cancer from radiation exposure is perhaps 1 percent, Beyea said.

"The individual risk will likely be low, but not the cumulative social risk," Beyea said.

"If they even look at that — no, no, no," said Terrie Barrie, a resident of Craig, Colorado, and an advocate for her husband and other workers at the now-closed Rocky Flats nuclear-weapons plant, where the U.S. government is compensating certain cancer victims regardless of their history of exposure.

"There's no reason not to protect people as much as possible," said Barrie.

U.S. agencies for decades have followed a policy that there is no threshold of radiation exposure that is risk-free.

The National Council on Radiation Protection and Measurements reaffirmed that principle this year after a review of 29 public health studies on cancer rates among people exposed to low-dose radiation, via the U.S. atomic bombing of Japan in World War II, leak-prone Soviet nuclear installations, medical treatments and other sources.

Twenty of the 29 studies directly support the principle that even low-dose exposures cause a significant increase in cancer rates, said Roy Shore, chief of research at the Radiation Effects Research Foundation, a joint project of the United States and Japan. Scientists found most of the other studies were inconclusive and decided one was flawed.

None supported the theory there is some safe threshold for radiation, said Shore, who chaired the review.

If there were a threshold that it's safe to go below, "those who profess that would have to come up with some data," Shore said in an interview.

"Certainly the evidence did not point that way," he said.

The U.S. Food and Drug Administration, which regulates electronic devices that emit radiation, advises, broadly, that a single CT scan with a dose of 10 millisieverts may increase risks of a fatal cancer by about 1 chance in 2,000.

Supporters of the proposal say it's time to rethink radiation regulation.

"Right now we spend an enormous effort trying to minimize low doses" at nuclear power plants, for example, said Brant Ulsh, a physicist with the California-based consulting firm M.H. Chew and Associates. "Instead, let's spend the resources on minimizing the effect of a really big event."

Message

**From**: McClintic, Howard [McClintH@ctc.com]
**Sent**: 3/13/2018 4:07:47 PM
**To**: Konkus, John [konkus.john@epa.gov]
**Subject**: FW: Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!
**Attachments**: GAO report on Radiation Standards per EPA and NRC

Good Day Mr. Konkus,

When I read about your careful review of each and every Grant application (9/4/17 WPost article cited below), I decided that I would periodically communicate with you so that you would understand the relevance and importance of our linear no-threshold (LNT) Project as it relates to the Mission and Goals of the Trump Administration and, most importantly, to the EPA.

There is only one way to get rid of the LNT, which is "why" my colleague, Dr. Robert (Bob) Golden and I have embarked on the route that we are taking. The "path" to ridding the EPA (and the rest of the world) of the LNT albatross is to have the National Academy of Sciences (NAS) determine that prospective EPA rules and regulations can/should/must be science-based, not mathematically determined. The latter approach is unnecessarily expensive and burdensome, as the attached GAO (General Accountability Office) Report details. The GAO Report was sent to us by former Assistance Secretary for Nuclear Power at the DOE; Dr. Peter Lyons (https://www.energy.gov/contributors/peter-b-lyons) worked for US Senator Pete Domenici (R-NM) when I worked for US Senator Howard Baker (R-TN).

Please let me know "who" within EPA I should contact about additional funding for this initiative. Both Dr. Mike Honeycutt (SAB) and Dr. Edward Calabrese as well as Mike Nasi, among others, mentioned this Project to Administrator Pruitt; each of them would gladly repeat their support of this initiative to you and others. Our financial support has come from various foundations, coal companies and related associations, among others adversely impacted by the LNT in the US and Canada. Bob Golden and I would welcome the opportunity to have a Conference Call or meet with you.

I am grateful for your interest and responsiveness.

Most sincerely yours,

***Howard***

Ex. 6 Personal Privacy (PP)

https://www.washingtonpost.com/politics/epa-now-requires-political-aides-sign-off-for-agency-awards-grant-applications/2017/09/04/2fd707a0-88fd-11e7-a94f-3139abce39f5_story.html?tid=a_mcntx&utm_term=.f556ef9f6c4d

---

**From:** McClintic, Howard
**Sent:** Monday, March 12, 2018 4:57 PM
**To:** 'lynn.tricia@epa.gov'; Konkus.John@epa.gov
**Subject:** Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!

CTC Foundation

***Ensuring the Future Through Innovation, Science and Technology***

1235 S. Clark St. Ste. 715
Arlington, VA 22202
(703) 310-5688 (703) 310-5655 FAX
Ex. 6 Personal Privacy (PP)
E-Mail: McClintH@ctc.com
Ex. 6 Personal Privacy (PP)

Good Day Ms. Lynn:

My colleague, Dr. Robert (Bob) Golden, and I would like to schedule some time soon to have a Conference Call with you and **John Konkus**. We want you to clearly understand our Goals and Objectives as well as the importance and purpose of our soon to be completed peer-reviewed Science Committee Report.

Toward this end, I am attaching my PowerPoint Presentation. Bob and I each realize that slides 7 through 11 as being the most important because they visually depict the distortive effects of the LNT sharply contrasted with (and compared to) science-based data points. As you are aware, even now and through time, the former EPA Administrator, Gina McCarthy, consistently and emphatically repeats in interviews as well as in testimony over four years ago (on November 14, 2013), before the US House of Representatives Committee on Science, Space and Technology, she testified:

> "...Let me begin by stating that science is and has always been the backbone of the EPA's decision-making. The Agency's ability to pursue its mission to protect human health and the environment depends upon the integrity of the science upon which it relies. I firmly believe that environmental policies, decisions, guidance, and regulations that impact the lives of all Americans must be grounded, at a most fundamental level, in sound, high quality, transparent, science..."

(https://science.house.gov/sites/republicans.science.house.gov/files/documents/HHRG-113-SY-20131114-SD001%20.pdf as well as http://www.c-span.org/video/?327016-1/epa-administrator-gina-mccarthy-testimony-proposed-regulations

As you know, the Goal of this project is to determine, through a rigorous analyses of both the radiation and chemical data, the comparative validity of the science. The ***CTC Foundation's*** Science Committee that will compare and contrast the scientific evidence for the LNT and threshold models for radiation- and chemical-induced cancer and non-cancer effects in humans. This Committee was empaneled in October, 2016 and is comprised of recognized experts, from diverse disciplines and backgrounds. Their purpose is to develop a comprehensive peer-reviewed publication. Bob Golden and Dr. Edward Calabrese (https://www.umass.edu/sphhs/person/faculty/edward-j-calabrese) are Co-Chairs of the Science Committee.

We look forward to our Conference Call as soon as possible. We are very grateful for your time, attention and assistance – Thank You.

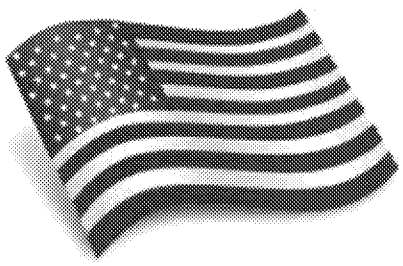
Most sincerely yours,

***Howard***

Howard G. McClintic

Executive Director

Ex. 6 Personal Privacy (PP)



This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

www.ctc.com 1-800-282-4392

United States General Accounting Office

GAO

Report to the Honorable
Pete Domenici, U.S. Senate

June 2000

# RADIATION STANDARDS

# Scientific Basis Inconclusive, and EPA and NRC Disagreement Continues

GAO

Accountability * Integrity * Reliability

GAO/RCED-00-152

ED_002751_00006820-00001

# Contents


## Letter 3

## Appendixes

Appendix I: Scope and Methodology 32
Appendix II: Major U.S. Radiation Standards 34
Appendix III: Examples of Different Models of Low-Level Radiation Effects 35
Appendix IV: Overview of Epidemiological Research on Low-Level Radiation Effects 36
Appendix V: Costs of Different Radiation Standards 40
Appendix VI: Comments From the Environmental Protection Agency 46
Appendix VII: Comments From the Nuclear Regulatory Commission 56
Appendix VIII: Comments From the Department of Energy 58

## Tables

Table 1: Estimated Costs to Achieve Different Soil Cleanup Levels at Selected DOE Sites and Generic NRC-Licensed Sites 27
Table 2: Potential Costs to Achieve Different Soil Cleanup Levels—DOE's, NRC's, and EPA's Analyses 41

## Figures

Figure 1: The Linear, No-Threshold Model of Low-Level Radiation Effects 11
Figure 2: Four Models of Low-Level Radiation Effects 35
Figure 3: Cleanup Costs as a Function of Cleanup Levels—Hazardous Waste Facility, Brookhaven National Laboratory, 1998 43


### Abbreviations

| | |
|---|---|
| DOE | Department of Energy |
| EPA | Environmental Protection Agency |
| GAO | General Accounting Office |
| NRC | Nuclear Regulatory Commission |



ED_002751_00006820-00003

ED_002751_00006820-00004

GAO
Accountability * Integrity * Reliability

United States General Accounting Office
Washington, D.C. 20548

Resources, Community, and
Economic Development Division

B-284378

June 30, 2000

The Honorable Pete Domenici
United States Senate

Dear Senator Domenici:

As the cold war came to a close, the United States shifted its focus from producing nuclear weapons to cleaning up its nuclear weapons production facilities. The Department of Energy (DOE), which manages the U.S. nuclear weapons program, is now cleaning up over a dozen major weapons production sites around the country. In addition, the nation's nuclear power industry is starting to decommission over 100 commercial nuclear power plants located in 31 states, a task that will continue during the coming decades. Furthermore, DOE is determining the feasibility of constructing an underground repository to provide for permanently disposing of much of the nation's highly radioactive waste at Yucca Mountain, Nevada. Until a repository is operational, federal facilities and nuclear power plants across the country will continue to store their highly radioactive waste on-site.

What standards should be used to protect the public from the risks of exposure to low-level radiation remaining at these sites after the nuclear materials and wastes have been removed—or, in the case of Yucca Mountain, to protect the public from exposure to the buried waste—is a question for which two federal agencies share primary responsibility. The Environmental Protection Agency (EPA) issues generally applicable public radiation protection standards and administers the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (Superfund), which governs cleanups of federal and nonfederal facilities. The Nuclear Regulatory Commission (NRC) issues implementing radiation protection standards as part of its mandate to regulate civilian sources of nuclear radiation, and it oversees the decommissioning of commercial nuclear facilities. The states may also be involved in radiation protection efforts under agreements with NRC for nuclear facilities within their jurisdictions. Finally, the National Academy of Sciences has a congressionally mandated role in recommending radiation protection standards for the Yucca Mountain repository.



ED_002751_00006820-00005

Historically, EPA and NRC have sometimes differed over how restrictive U.S. radiation protection standards should be, as we reported in 1994.[1] These differences have implications for the pace and cost of federal facility cleanups and commercial decommissioning efforts, as well as for the design and potential development of the Yucca Mountain repository. Concerned about these issues, you asked us to examine the scientific basis for the agencies' radiation protection standards and the costs of implementing them. As agreed with your office, this report examines (1) whether the current U.S. radiation protection standards have a well-verified scientific basis, (2) whether federal agencies have come closer to agreeing on standards since we reported on this issue in 1994, and (3) how implementing these standards may affect the costs of nuclear waste cleanup and disposal activities. During our review, we examined many scientific studies and obtained the views of recognized scientists on the scientific basis of radiation standards. We focused mainly on differences in standards for Yucca Mountain and nuclear cleanup and decommissioning sites because they are prominent current examples of the debate about standards. In addition, the report includes a review, performed by a recognized expert in environmental radiation, of scientific research correlating naturally occurring (background) radiation levels in the United States and around the world with local cancer rates. This review was designed to determine whether the research results might have implications for setting radiation protection standards. (See app. I for a detailed discussion of our scope and methodology.)

## Results in Brief

U.S. regulatory standards to protect the public from the potential health risks of nuclear radiation lack a conclusively verified scientific basis, according to a consensus of recognized scientists. In the absence of more conclusive data, scientists have assumed that even the smallest radiation exposure carries a risk. This assumption (called the "linear, no-threshold hypothesis" or model) extrapolates better-verified high-level radiation effects to lower, less well-verified levels and is the preferred theoretical basis for the current U.S. radiation standards. However, this assumption is controversial among many scientists. Some say that the model is overly conservative and that below certain exposure levels, there is no risk of cancer from radiation. Others say that the model may underestimate the risk. The research evidence is especially lacking at regulated public

[1] *Nuclear Health and Safety: Consensus on Acceptable Radiation Risk to the Public Is Lacking* (GAO/RCED-94-190, Sept. 19, 1994).



ED_002751_00006820-00006

exposure levels—levels of 100 millirem a year and below from human-generated sources. Interest among scientists in obtaining a more conclusive understanding of the effects of low-level radiation has been evident in recent federally funded initiatives, including a reassessment by the National Academy of Sciences of the latest research evidence on the risks of low-level radiation, begun in the summer of 1998 and planned to conclude in 2001. Also, a 10-year DOE research program, begun in fiscal year 1999, has been specifically addressing the effects of low-level radiation within human cells, in part to help verify or disprove the linear model.

Lacking conclusive evidence of low-level radiation effects, U.S. regulators have in recent years set sometimes differing exposure limits. In particular, EPA and NRC have disagreed on exposure limits. Although we recommended as far back as 1994 that the two agencies take the lead in pursuing an interagency consensus on acceptable radiation risks to the public, they continue to disagree on two major regulatory applications: (1) the proposed disposal of high-level nuclear waste in a repository at Yucca Mountain and (2) the cleanup and decommissioning of nuclear facilities. Centrally at issue between the two agencies is groundwater protection. On the one hand, EPA applies community drinking water limits for radioactive substances to groundwater at nuclear sites, as a matter of water resource protection policy. Some of these limits are equivalent to fractions of a millirem a year. On the other hand, NRC includes groundwater and other potential contamination sources under a less restrictive limit of 25 millirem a year for all means of exposure,[2] an approach that conforms to internationally recommended radiation protection guidance. As applied in proposed standards for nuclear waste disposal at Yucca Mountain, EPA's groundwater approach has been criticized as technically unsupported by the National Academy of Sciences, which the Congress mandated to recommend standards for the repository. However, the Academy recognizes that EPA has the authority to establish a separate groundwater limit for Yucca Mountain, and EPA believes its groundwater protection approach for the repository to be technically justified. As applied to nuclear cleanup and decommissioning sites where both EPA and NRC may have jurisdiction, the two agencies' different regulatory approaches have sometimes raised questions of inefficient, conflicting, dual regulation. There has been little progress in finalizing a memorandum of

[2]These means of exposure, called "pathways" by specialists, include exposure through soil, water, and air.



ED_002751_00006820-00007

understanding, encouraged by the House Appropriations Committee in August 1999, to resolve EPA's and NRC's conflict about cleanup standards. Given their historical differences, EPA and NRC may not easily agree on groundwater protection standards for Yucca Mountain or on their respective regulatory roles relating to nuclear cleanup and decommissioning sites. This report contains a matter for congressional consideration suggesting that, in such a situation, the Congress may wish to help resolve the agencies' disagreement.

The costs of implementing different radiation standards vary, depending on the standards' restrictiveness. Generally, the costs increase as the standards become more restrictive. Comprehensive estimates of overall costs to comply with current and prospective standards were unavailable, but these costs could be immense, considering that federal agencies expect to fund hundreds of billions of dollars in nuclear waste disposal and cleanup projects over many years in the future. According to DOE's and NRC's analyses of cleanup options for individual sites, costs per site can be many millions of dollars higher to comply with more restrictive standards than less restrictive standards, as might be expected. For example, a 1995 DOE analysis of cleanup options for plutonium-contaminated test ranges at the Nevada Test Site estimated $35 million in costs to achieve a 100-millirem-a-year-level, over three times as much to achieve a 25-millirem-a-year level, and over six times as much to achieve a 15-millirem-a-year level. Finally, the analysis showed costs that were over 28 times higher to achieve a 5-millirem-a-year level, illustrating that compliance costs accelerate rapidly to achieve the most restrictive protection levels.

We presented a draft of this report to NRC, DOE, and EPA for comment. NRC found the report to be fundamentally sound, and DOE found it to be factual and balanced. EPA disagreed with the report's conclusions, particularly our conclusion that there has been little progress on the finalization of a memorandum of understanding to resolve EPA's and NRC's conflict about cleanup standards. However, although the two agencies are developing such a memorandum, they have had long-standing differences, and we question whether their latest efforts will resolve these differences without congressional intervention. All three agencies provided technical comments on the report. In response to the comments received, we made some changes to the report's presentation.



ED_002751_00006820-00008

## Background

Nuclear radiation can be generally categorized as either low-level or high-level radiation. The low-level range includes exposures up to about 10,000 total millirem, [3] although the term commonly is used to refer to exposures of a few hundred millirem or less.[4] The lower portion of the low-level range includes natural background radiation levels, and the lowest portion of this range includes public exposure levels regulated under various U.S. radiation standards, as shown in appendix II.[5] Natural background radiation levels vary around the world, from below 100 millirem of exposure a year in some places to several hundred millirem a year in others, with even higher levels recorded in "hot spots." In the United States, average natural background radiation exposure is about 300 millirem a year. In addition, medical practices, such as X-rays and nuclear medicine, and industrial nuclear operations contribute average public exposures of about 50 millirem a year and 0.1 millirem a year, respectively. Radiation from within one's own body, largely from naturally present radioactive potassium, contributes almost 40 millirem a year, on average. As shown in appendix II, regulatory public exposure limits vary from a few millirem a year up to 100 millirem a year. At these levels, radiation is only one of many environmental and biological events (such as heat) that may alter (mutate) cell structure, and low-level radiation is commonly considered to be a relatively weak source of cancer risk.[6] To counter these cellular-level mutations, the human body has active repair processes, although these processes are not entirely error-free, and their relevance to human cancer risk remains unclear. Should a radiation-caused cancer develop in one or more cells, the process may take years, and the source of the cancer will be verifiable only in exceptional cases, given the current limited

[3]A millirem is a commonly used unit of measurement of the biological effect of radiation. The radiation from a routine chest X-ray is equivalent to about 6 millirem.

[4]Above about 30,000 total millirem, radiation exposure is a well-known cause of cancer. Instantaneous (or short-duration) exposures of about 200,000 total millirem can cause blood cell changes, infections, and temporary sterility. Short-duration exposures above about 400,000 total millirem can cause death within days or a few weeks and are associated with catastrophic nuclear accidents or atomic bomb blasts.

[5]U.S. worker protection standards limit annual exposures to 5,000 millirem. See app. II.

[6]About 187,000 spontaneous cell-altering events occur daily in each human cell. Low-level radiation exposures increase the number of such events by a small fraction—about 1 percent. There is evidence that the type of damage done by such radiation has a higher probability of resulting in DNA misrepair than the type of damage done by other normally occurring cell-altering events.



ED_002751_00006820-00009

understanding of how cancer develops. Although nearly one in four persons in the United States dies of cancer from all causes, low-level radiation presumably accounts for a very small fraction of these cancers, if any. However, the fraction cannot be quantified.

Federal agencies, and in some instances states, administer U.S. radiation standards. EPA and NRC administer the majority of the federal standards. EPA issues environmental radiation protection standards as mandated under Presidential Reorganization Plan No. 3 of 1970. NRC issues standards as part of its mandate to regulate civilian sources of nuclear radiation, under the Atomic Energy Act. (Under the same act, DOE has issued public and worker exposure limits applicable on-site at the agency's nuclear installations.) Both EPA and NRC have regulatory roles related to nuclear waste disposal and nuclear site cleanup and decommissioning. For example, under the Energy Policy Act of 1992, both have roles at the proposed Yucca Mountain repository in southern Nevada. The proposed function of the repository is to receive and dispose of high-level waste from DOE sites and commercial power plants around the country. EPA has the role of issuing standards to protect the public from releases of radioactive materials from the facility, and NRC has the role of issuing technical requirements and criteria and licensing the facility. Under the act, exposure limits in NRC's final technical requirements and criteria are to be consistent with the limits in EPA's final public protection standards. DOE's role at Yucca Mountain will be as the developer and prospective operator of the repository, and the Department is pursuing the goal of deciding in 2001 whether to recommend the site to the President as suitable for nuclear waste disposal. Also involved in Yucca Mountain oversight are expert advisory bodies, including the Nuclear Waste Technical Review Board and the National Academy of Sciences, which was mandated under the Energy Policy Act of 1992 to recommend standards for the repository. In regard to nuclear cleanup and decommissioning activities, both EPA and NRC have mandated roles: EPA administers Superfund, the legislation that governs cleanups of federal and nonfederal facilities, and NRC regulates the



ED_002751_00006820-00010

decommissioning of over 100 active commercial nuclear power plants, as well as other commercial nuclear facilities, under the Atomic Energy Act.[7,8]

Our September 1994 report on radiation protection issues found that U.S. radiation standards reflected a lack of federal agency consensus on acceptable radiation risk to the public, as well as a lack of interagency coordination on standards. Among the reasons we found for the lack of consensus were differences in agencies' historical missions and legislative mandates, as well as differences in agencies' regulatory strategies, particularly in those of EPA and NRC. For example, EPA has historically in many cases implemented a risk-based radiation protection approach, under which the agency addresses individual contamination sources, coregulates chemicals and radioactive substances, and protects both human health and environmental resources.[9] In accordance with its tradition of regulating chemicals, EPA has generally set a risk of 1 in a million that an individual will develop cancer in a lifetime as a goal for remediation and has considered a risk of greater than 1 in 10,000 to be potentially excessive. EPA's approach has been described as "bottom up," setting a relatively restrictive risk goal to be pursued through the best available technology—but allowing less restrictive limits in site-specific situations. In contrast, NRC favors a dose-based, radiation-specific protection approach that focuses on human health protection.[10] NRC's protection strategy has been

[7]Superfund regulations call for, among other steps, the development of cleanup alternatives through a remedial investigation, the finalization of applicable cleanup requirements, and a formal record of decision on an agreed cleanup level, after which cleanup is conducted. Decommissioning involves the removal of all radioactive components and materials from the facility and the cleanup of radionuclides to NRC's standards (10 C.F.R. 20).

[8]The coordination of federal radiation protection issues is the responsibility of the federal Interagency Steering Committee on Radiation Standards, and coordination among states is the responsibility of the Conference of Radiation Control Program Directors. In addition, authoritative national and international technical organizations make recommendations on radiation protection issues, including the congressionally chartered U.S. National Council on Radiation Protection and Measurements, the International Commission on Radiological Protection, and the United Nations Scientific Committee on the Effects of Atomic Radiation.

[9]EPA's protection approach draws, in part, on experience with regulating thousands of different chemicals, many of which pose risks that are generally thought to be even less well understood than radiation risks. These chemicals may or may not exist naturally in the environment.

[10]NRC's approach (with which DOE generally concurs) draws on experience in estimating radiation-specific risks, within an internationally recommended radiation dose limitation and risk assessment framework. The framework takes into account that radiation exists naturally in the worldwide environment.



ED_002751_00006820-00011

described as a "top down" approach. Compared with EPA, NRC sets a relatively less restrictive dose limit but reduces doses (and risks) well below the limit in site-specific situations where the reductions are "reasonably achievable."[11]

## U.S. Public Radiation Protection Standards Lack a Conclusive Scientific Basis

The standards administered by EPA and NRC to protect the public from low-level radiation exposure do not have a conclusive scientific basis, despite decades of research. These standards are based on a hypothetical model of low-level radiation effects. The model, derived from studies of large populations (in the tens of thousands) exposed to radiation, extrapolates better-verified high-level radiation effects to lower, less well-verified levels. The standards protect at annual millirem levels considerably lower than the better-verified levels. According to a consensus of scientists, there is a lack of conclusive evidence of low-level radiation effects below total exposures of about 5,000 to 10,000 millirem. The model under which these effects are assumed, lacking conclusive evidence, is called the "linear, no-threshold" hypothesis or model. According to this model, even the smallest radiation exposure carries a quantifiable cancer risk. The model, which has been endorsed by national and international radiation protection organizations and used for many years as a preferred model in regulating low-level radiation, is a fundamental basis for U.S. radiation standards. There is interest among scientists in obtaining more conclusive evidence of radiation effects, and a DOE research program that is examining cellular low-level radiation effects may eventually help to develop a better understanding of the cellular processes of radiation cancer causation.

### Low-Level Radiation Effects Are Assumed for Regulatory Purposes

Conclusive evidence of radiation effects is lacking below a total of about 5,000 to 10,000 millirem, according to the scientific literature we examined and a consensus of scientists whose views we obtained. At these

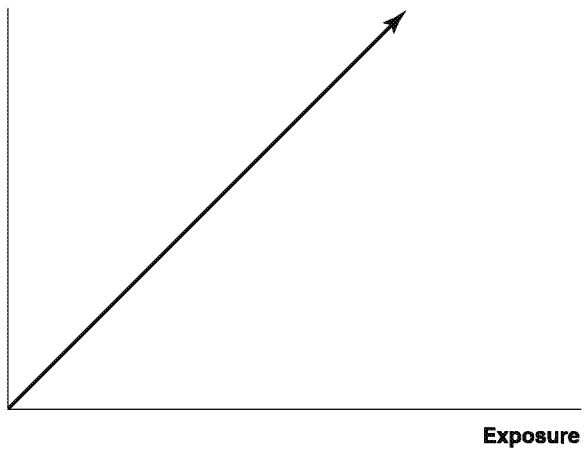
[11]NRC's 25-millirem-a-year dose limit is equivalent to 1 chance in about 1,000 of a fatal cancer over a 70-year lifetime, using a commonly accepted dose-risk conversion factor and assuming the linear model of radiation effects holds.



ED_002751_00006820-00012

levels, authoritative bodies have estimated radiation risks through complex modeling of the available data,[12] and regulators have assumed that even the smallest radiation exposure carries a risk. This assumption is commonly referred to as the linear, no-threshold hypothesis or model. Extrapolated mainly from high-dose effects reported for Hiroshima and Nagasaki survivors, the linear model assumes that radiation health effects are proportional to exposure. As figure 1 shows, the model uses a straight line to extrapolate risks all the way down to zero. From zero upward, the model assumes that as exposure doubles, risk doubles, and that no entirely risk-free exposure level or threshold exists.

**Figure 1: The Linear, No-Threshold Model of Low-Level Radiation Effects**




Radiation protection organizations such as the National Council on Radiation Protection and Measurements and the International Commission on Radiological Protection have historically endorsed the model, and U.S. regulators have used it as a preferred, plausible model, but it is controversial. On the one hand, the model is widely considered to be a useful, relatively mathematically simple working hypothesis that may be

[12]For example, a 1990 study by a National Academy of Sciences committee, called BEIR V, estimated that, at the 90-percent statistical confidence interval, out of 100,000 adults exposed to 100 millirem a year of radiation over a lifetime, anywhere from 410 to 980 men and 500 to 930 women might die of cancer caused by the exposure. This confidence interval assumes the validity of the linear model and reflects the uncertainty of inputs to the model.



ED_002751_00006820-00013

conservative—that is, it may not underestimate risks. Regulators make use of the model in doing risk assessments, regulatory impact analyses, cost-benefit analyses, and other studies to support their decision-making. In using the model, they are able to estimate risk reductions and hypothetical lives saved from regulating at a given exposure level. On the other hand, many scientists question the validity of the model. The consensus view we encountered is that the research data on low-level radiation effects are inadequate either to establish a safety threshold or to exclude the possibility of no effects. Scientists we contacted and scientific literature we examined generally did not indicate that any one model clearly best fit the overall data. Instead, there was evidence that any of several models may "fit." (See app. III.) Some researchers also said low-level radiation effects are likely too complicated and variable to be expressed in a single model. There is evidence that the relationship may vary in individuals, and with the type of radiation, type of cancer, body organs exposed, sex, and/or age at exposure. We also found considerable agreement among regulators and scientists that the linear model may be a conservative "fit" to the data, unlikely to underestimate risks. However, some said the data support the existence of a safety threshold below which there are no risks, and others said low levels of radiation can be beneficial to health. This is a highly controversial theory, called hormesis, which is in part based on the documented ability of the body to repair cell damage—referred to as adaptive response. However, other scientists pointed to studies indicating the linear model may actually understate radiation risks, especially to fetuses and children.[13]

Authoritative radiation protection organizations and committees have given the linear model a qualified endorsement. For example, in 1990, a committee of the National Academy of Sciences, the Biological Effects of Ionizing Radiation Committee (BEIR V), reported that the linear model was not inconsistent with the available research data. According to the committee's report, at low radiation exposures, risks either less or greater than linearity—and the existence of a threshold in the low-level dose range—cannot be excluded, and "the possibility that there may be no risks from exposures comparable to external natural background radiation cannot be ruled out. At such low doses, it must be acknowledged that the lower limit of the range of uncertainty in the risk estimates extends to zero." In addition, a 1994 report of the United Nations Scientific Committee

[13]There is evidence of mental retardation linked to fetal exposure to low-level radiation. Age at time of exposure appears to be an important determinant of cancer risk from radiation.



ED_002751_00006820-00014

on the Effects of Atomic Radiation (UNSCEAR) stated that "there are theoretical reasons based solely on the nature of DNA damage and repair to expect that cancer can occur at the lowest doses without a threshold in the response, although this effect would perhaps not be statistically demonstrable."[14] Despite the linear model's unproven and controversial status among scientists, some scientists said the model is so well accepted that it could only be superseded on the basis of overwhelming contrary evidence.

## Research Efforts to Verify Low-Level Radiation Effects Are Ongoing

Two types of important research into low-level radiation effects have been conducted. One type of study painstakingly follows the long-term health of individuals in large populations exposed to radiation, seeking statistically significant patterns of elevated cancer risks from the radiation exposures. These are called epidemiological studies. Another type of study subjects animals or tissue or cell cultures to radiation, seeking biological evidence of radiation effects. These are called radiobiological studies.

Epidemiological studies may never conclusively prove or disprove the linear model, according to some scientists. Epidemiological studies have been a key basis for the linear model, including the research evidence accumulated on over 85,000 Japanese survivors of the Hiroshima and Nagasaki bomb blasts. The study, conducted by the international Radiation Effects Research Foundation, has well established the effects of radiation at high exposure levels, and scientists have extrapolated this relationship to the low-level radiation range as well—with considerable inherent uncertainty.[15] However, some scientists have questioned the project's results, asserting among other concerns that the basic estimates of the Hiroshima and Nagasaki doses (and their neutron component, for example) still need to be reevaluated, even after decades of effort devoted to determining these doses.

As noted, epidemiological studies require large study populations for the research results to be statistically powerful. Epidemiologists consider two

[14]The British National Radiation Protection Board similarly maintains, in consideration of relevant cellular and molecular data, that the weight of evidence falls decisively in favor of the thesis that for a majority of common human tumors, low-dose and low-dose-rate cancer risk rises as a simple function of dose with no threshold.

[15]According to one expert, extrapolating effects from high exposures to low exposures equivalent to natural background radiation levels is more guesswork than science.



ED_002751_00006820-00015

types of epidemiological studies—analytic or ecologic. Analytic studies either compare individuals who have been exposed to radiation to individuals who have not been exposed and determine if there are subsequent differences in their health status (cohort studies) or compare individuals who have a disease to those who do not to determine if there were differences in the past exposures of the two groups (case control studies). Ecologic studies rely on regional data on disease and radiation levels, instead of individual data, and are considered to be less reliable than analytic studies. Analytic and ecologic studies have attempted to correlate regional natural background radiation levels with regional cancer rates at locations in the United States, Europe, Asia, Brazil, Iran, and other places. A premise related to such studies is that, if the linear model holds, cancer rates should be higher at locations where natural background radiation levels are significantly higher. With the help of an expert consultant, we examined 82 studies, which generally found little or no evidence of elevated cancer risks from high natural background radiation levels. A large number of studies reported a lack of evidence of cancer risks, some others reported evidence of slightly elevated risks, and some others reported evidence of slightly reduced risks. Overall, the studies' results are inconclusive, but they suggest that at exposure levels of a few hundred millirem a year and below, the cancer risks from radiation may be either very small or nonexistent. (See app. IV.)

Radiobiological studies, particularly molecular studies, may eventually develop more conclusive scientific evidence of low-level radiation effects than epidemiological studies, according to scientists. Past radiobiological research has helped to establish, among other evidence, the genetic effects of radiation and its effects on individual body organs. Recently, there has been interest in research into the cellular processes through which radiation causes cancer, in part in relation to progress in human genome research in the 1990s.[16] Researchers have been obtaining a better understanding of specific phenomena such as DNA damage and repair, chromosomal instability, so-called "bystander" effects on neighboring cells, and cellular adaptation to exposures. Researchers are looking into such cellular processes for biological signs (or "biomarkers") of radiation cancer causation. Several stages are apparent in the development of radiation-caused cancer: DNA damage, misrepair, cancer initiation, cell proliferation, and tumor promotion (with subsequent malignant transformation). To date, the first stage in the process is better understood than the long-term second

[16]Such research focuses on cells' nuclei, where DNA is located.



ED_002751_00006820-00016

stage. Since fiscal year 1999, DOE has funded a research program targeting the biological effects of low-level radiation at the cellular level, with total funding of almost $220 million projected over 10 years. The program is considered unique in that it is designed specifically to better validate the effects of very low levels of radiation in areas such as cells' response to radiation damage, thresholds for low-dose radiation effects, and features distinguishing radiation-caused cell damage from damage from causes internal to the cell. Many scientists and regulators we interviewed said this type of research could eventually help to determine more conclusively the effects of low-level radiation and their potential link to cancer causation.

In October 1998, the National Academy of Sciences contracted to reassess the linear model and risk estimates for low-level radiation, at the request of U.S. regulators, including EPA, NRC, and DOE. The regulators, acting through the Interagency Steering Committee on Radiation Standards, concluded that enough research progress had been made in the 1990s to warrant the study. The Academy last did such an assessment in 1990, called BEIR V. The latest assessment, called BEIR VII, is to be completed by 2001.[17] High expectations have been set for the BEIR VII committee, reflecting the scientific controversy surrounding the linear model and low-level radiation effects. For example, in requesting the effort, EPA, DOE, and NRC asked the committee to focus on areas the agencies do not believe were emphasized in the previous BEIR V effort. EPA asked the committee to provide a clear indication of the weight of evidence for risks at low doses and dose rates and to carefully assess the sources of any inconsistencies in the results from different epidemiological studies. DOE asked BEIR VII to consider epidemiological studies on nuclear workers, and NRC asked the committee to focus especially on evidence of radiation effects at the lowest portion of the low-level radiation range, at levels where regulators set radiation standards, and to consider evidence of hormesis. Also, the committee is committed to fully assessing all pertinent research data, not just the data that have been traditionally influential, such as the Hiroshima and Nagasaki data. Because of its broad focus, the BEIR VII assessment could produce instructive results, but some agency officials and scientists said the amount of new research data available might not be sufficient to lead the committee to either fully validate or disprove the linear model. An EPA official said he expected the BEIR VII work to support the continued use of the linear model for regulatory purposes.

[17]BEIR VI was a 1999 Academy assessment of risks from radon.



ED_002751_00006820-00017

## EPA and NRC Continue to Disagree on Major Radiation Standards for Public Protection

We reported in 1994 that federal agencies' radiation standards reflected a lack of consensus on acceptable risk to the public. Today, this situation persists, and EPA and NRC, the principal federal radiation standard-setting agencies, continue to disagree significantly on regulatory approaches and standards related to groundwater protection. Two major instances of their disagreement are proposed standards for the prospective Yucca Mountain high-level-waste repository and standards for the cleanup and decommissioning of federal and commercial nuclear facilities. For these applications, EPA favors both (1) a public protection limit of 15 millirem a year from all radiation sources through all means of exposure—called "all pathway" protection by specialists—and (2) extra protection of groundwater resources under sites, at limits originally set for community drinking water systems, equivalent to 4 millirem a year. Alternatively, NRC favors a single 25-millirem-a-year all-pathway public protection limit, within which groundwater is a potential pathway.[18] This disagreement has complicated planning for the prospective Yucca Mountain high-level waste repository, on which a national decision is to be made in 2001, as well as day-to-day planning for facility decommissioning by commercial nuclear operators licensed by NRC. In both of these cases, it remains to be seen whether EPA and NRC can resolve their differences or whether the Congress will need to intervene.

### EPA and NRC Have Proposed Different High-Level-Waste Disposal Standards

The disagreement between EPA and NRC on groundwater protection is reflected in differences in the radiation standards set by the two agencies but appears most notably in the debate over proposed draft standards for the Yucca Mountain, Nevada, high-level-waste repository. Radiation standards are an important part of the ongoing debate about the future of the planned facility. Both EPA and NRC issued proposed radiation protection standards for the repository in 1999, NRC in February and EPA in August. The agencies differ on proposed all-pathway limits (15 millirem a year versus 25 millirem a year), and especially on extra groundwater protection. The groundwater issue at Yucca Mountain relates to differences in the two agencies' overall resource protection policies, as well as technical details. EPA's approach reflects its attempt to implement a

[18]EPA's approach includes various levels of acceptable risk, from 1 chance in about 2,000 to less than 1 chance in about a million of a fatal cancer over a 70-year lifetime. NRC's all-pathway approach involves a level of acceptable risk of 1 chance in about 1,000 of a fatal cancer over a lifetime. These calculated risks are based on a commonly used dose-risk conversion factor, assuming the linear model holds.



ED_002751_00006820-00018

consistent policy, across various standards, of protecting groundwater as a national resource, in line with community drinking water standards established in regulations under the Safe Drinking Water Act. (According to EPA, the policy is based on preventing pollution before it occurs. If pollution has occurred, the polluter should be responsible for the costs of cleanup.) On the other hand, NRC believes its all-pathway approach is fully protective of human health at Yucca Mountain and elsewhere. In the Commission's view, EPA's drinking water standards were not originally intended for an application such as Yucca Mountain, and the Commission questions EPA's technical basis for proposing extra groundwater protection.[19,20]

NRC has been joined in its views by DOE and some others who have commented on EPA's proposed Yucca Mountain standards, including the National Academy of Sciences. The Academy has questioned the technical basis for EPA's extra groundwater protection approach. Specifically, the Academy, together with NRC, DOE, and other commenters, has asserted, first, that EPA has not provided a technical rationale for its approach. By contrast, according to these commenters, NRC has a technically based rationale for its approach that is in accord with internationally recommended radiation protection practices. Second, the Academy and others have pointed out that the drinking water concentration limits to be applied to groundwater at the repository are outdated, reflecting doses and risks that are inconsistent. These limits consist of dozens of numerical maximum contaminant levels for radionuclides, expressed in picocuries per liter, which reflected consistent doses and risks when they were

[19]The agencies also disagreed on low-level waste disposal standards in the mid-1990s. Current low-level waste standards consist of NRC's 25-millirem-a-year all-pathway limits that date from 1983. In 1994, EPA considered issuing its own standards, reflecting 15-millirem-a-year all-pathway protection, plus extra groundwater protection to drinking water standards. At the time, DOE estimated over $300 million in added annual costs if its disposal sites and commercial disposal sites were required to comply with the approach EPA was considering.

[20]In addition, in 1994, EPA issued transuranic waste disposal standards for the Waste Isolation Pilot Project in southeastern New Mexico (40 C.F.R. 191) that include 15-millirem-a-year all-pathway limits, plus extra groundwater protection to drinking water standards. NRC expressed concerns about the groundwater protection standards but concurred with them because on-site groundwater was not an issue in EPA's project certification process—the aquifer was brine. Transuranic waste is tools, rags, laboratory equipment, and other items contaminated with radioactive elements, mostly plutonium.



ED_002751_00006820-00019

established in regulations implementing the Safe Drinking Water Act of 1976.[21] These limits are outdated under the latest risk estimation methods.

In particular, the Academy, in its congressionally-mandated role of recommending reasonable standards for protecting health and safety at the repository, has questioned EPA's groundwater protection approach for Yucca Mountain. The Academy did not propose separate groundwater protection standards for the repository in its own technical recommendations for the facility, which were issued in 1995. The Academy's November 1999 comments on EPA's draft standards directly opposed such an approach, calling it "scientifically unsupported," adding little or no public health benefit.[22] According to the Academy, EPA has the authority to establish a separate groundwater limit for Yucca Mountain but has not presented a technical rationale for doing so. In addition, NRC and DOE have commented that EPA has not done a comprehensive analysis of the health benefits and costs of its groundwater approach for Yucca Mountain. EPA has issued a draft regulatory impact analysis to accompany its draft Yucca Mountain standards, in accordance with Executive Order 12866, which calls for such an analysis if the regulatory action is significant (for example, raises novel legal or policy issues). However, the draft regulatory impact analysis was limited in scope (stating that data were lacking for a fuller discussion), and the document did not analyze the specific impact of EPA's groundwater protection approach for the repository.

EPA recognizes that the drinking water contamination limits that are to be applied at the repository are not scientifically up to date. They are based on 1970s-era methods of radiation dose estimation, which have been superseded. The limits were originally intended to be equivalent to 4 millirem a year of exposure. However, under updated dose estimation methods, they no longer reflect 4 millirem a year. Instead, using a commonly accepted dose conversion factor, they reflect varying annual millirem levels and acceptable risks, and some reflect millirem levels up to a thousand times lower than average U.S. natural background radiation levels. A few of the limits are equivalent to well above 4 millirem a year, but

[21]Under 40 C.F.R. 141, annual concentrations of beta particle and photon activity sources are limited to no more than a total body or internal organ dose equivalent of 4 millirem a year. See app. II.

[22]On the other hand, the Academy found the magnitude of EPA's proposed 15-millirem-a-year all-pathway limit to be consistent with the Academy's own recommendations.



ED_002751_00006820-00020

many are equivalent to fractions of a millirem a year.[23] NRC has commented that because groundwater is expected to be the dominant exposure pathway at Yucca Mountain, these limits will be the de facto overall protection standards for the repository.

According to EPA officials, the agency's proposed standards and groundwater protection approach for Yucca Mountain are justified on policy grounds and are technically justifiable as well. The agency has applied drinking water standards to groundwater at the repository, EPA officials said, because it desires to protect groundwater as an environmental resource (for drinking water and irrigation needs) in a region where the population has been growing quickly. In addition, the agency has a general policy of coregulating chemicals and radionuclides in groundwater, and EPA officials said the standards for Yucca Mountain should be in accord with this policy. EPA officials agreed that the agency has not done a comprehensive analysis of the health benefits and costs of the agency's groundwater approach for Yucca Mountain, but they believe their regulatory approach has fully addressed the pertinent overall technical issues related to setting radiation protection standards for the site. They said they are developing an expanded regulatory impact analysis to accompany their final standards, which will not constitute a specific technical rationale for their extra groundwater protection approach but will address technical and cost issues related to the implementation of their standards, as the Academy recommended.

While recognizing that the drinking water concentration limits to be applied at Yucca Mountain are out of date, reflecting inconsistent doses and risks, EPA officials said the agency is in the process of updating the limits and expects to complete this effort by the fall of 2000. They said that if the final Yucca Mountain standards are issued before then, the updated limits will be incorporated into them. The officials noted that under a "no backsliding" provision of the 1996 Safe Drinking Water Act Amendments, any updated drinking water standards for radionuclides must maintain

[23]For example, the limit for Iodine 129, considered a benchmark among the various limits for Yucca Mountain, is 1 picocurie per liter, or about 0.2 millirem a year; the limit for Nickel 63 is 50 picocuries per liter, or about 0.02 millirem a year, and the limit for Tritium is 20,000 picocuries per liter, or about 0.9 millirem a year. In addition, the limits reflect acceptable lifetime risks ranging anywhere from less than 1 chance in a million to more than 1 chance in 2,000 of a person dying from the exposure, using a commonly accepted dose-risk conversion factor and assuming the linear model holds. EPA points out that most limits fall within its acceptable risk range of 1 chance in about 10,000 to 1 chance in about a million of a person getting cancer from the exposure.



ED_002751_00006820-00021

equal or greater levels of public health protection. According to EPA, this provision precludes the agency from raising any of the concentration limits, even in attempting to achieve greater uniformity in doses or risks.[24] A draft version of the proposed new limits indicates that EPA may not change any of the limits.[25]

As EPA and NRC prepare to issue final standards for Yucca Mountain, it is not evident that the two agencies and the Academy will agree on appropriate groundwater protection standards for the repository. If they do not agree, EPA's final Yucca Mountain standards, expected to be issued in the summer of 2000, will lack a degree of technical consensus that would add to their credibility and acceptability. Aware of the conflict between EPA and NRC over standards for Yucca Mountain, the Congress, in March 2000, passed legislation retaining EPA's standard-setting authority while (1) allowing the Academy and NRC to report to the Congress any major disagreements they may have with EPA's final standards and (2) delaying the issuance of final standards for Yucca Mountain until June 2001. On April 25, 2000, the President vetoed the bill, in part because it would have limited EPA's authority to issue radiation standards, and on May 2, 2000, the Senate upheld the veto.

## EPA and NRC Have Issued Different Standards and Guidance for Nuclear Site Cleanup and Decommissioning

Both EPA and NRC developed nuclear site cleanup and decommissioning standards in the 1990s, attempting to facilitate the massive national effort to clean up nuclear contamination at many federal and commercial nuclear sites—including DOE's nuclear weapons complex and commercial nuclear power plants licensed by NRC —that are closing down after decades of operations. In 1995, EPA drafted cleanup standards reflecting the agency's groundwater protection approach, which includes 15-millirem-a-year all-pathway protection, plus separate groundwater protection to drinking water standards. However, the agency withdrew these standards in 1996, before they were finalized, after other agencies objected to them. Subsequently, in 1997, EPA implemented the same approach through

[24]Another technically related groundwater issue is EPA's prospective choice of a groundwater scenario for Yucca Mountain, including the point of enforcement (at or how near to the repository boundary) and appropriate estimated groundwater flow volume. DOE and NRC officials said a very conservative scenario could severely complicate DOE's efforts to do detailed, refined groundwater analysis for the site.

[25]According to EPA, the new limits are to be based on acceptable risks instead of the current dose basis of 4 millirem a year.



ED_002751_00006820-00022

nonbinding Superfund guidance. Also in 1997, NRC finalized its own cleanup standards—decommissioning standards for its licensees—reflecting 25-millirem-a-year all-pathway protection.[26] In correspondence with NRC, EPA has objected to NRC's standard as potentially not protective in all cases.[27] In some cases, both EPA's and NRC's approaches have both been applied to the same site, raising questions about potential dual regulation.

EPA and NRC have long disagreed on standards for cleaning up and decommissioning the nation's nuclear sites. As far back as 1992, the two agencies signed a memorandum of understanding, agreeing to avoid unnecessary duplication of regulatory requirements. In 1994, we reported that EPA and NRC were involved in potentially costly dual regulation of NRC's licensees. Our previous report's recommendation that the agencies pursue consensus on acceptable risk was a factor in the establishment in 1995 of the Interagency Steering Committee on Radiation Standards, which is cochaired by EPA and NRC. However, despite numerous staff initiatives and some progress in cooperation, this committee has not resolved major issues between the two agencies. The two agencies have continued to use separate approaches in setting standards for cleaning up and decommissioning nuclear sites, especially when groundwater protection is involved. Consequently, perceived dual regulation by EPA and NRC continues to complicate the cleanup and decommissioning process at some sites where both agencies' standards may apply, potentially causing duplication of effort and regulatory delays, adding to facilities' compliance costs, and raising public questions about what cleanup levels are appropriate and safe.[28]

[26]In addition, DOE has issued public protection orders for its nuclear installations that generally conform to NRC's approach, including all-pathway protection without extra groundwater protection, as well as dose reductions to levels as low as reasonably achievable. DOE has proposed to convert its order into a regulatory standard, but EPA has opposed the draft standard as inconsistent with Superfund requirements.

[27]In 1994, NRC considered standards comparable to EPA's—15 millirem a year, with separate groundwater protection to drinking water standards—but changed to an all-pathway, 25-millirem-a-year approach after further analysis and public comments on the proposed rule.

[28]Also, over the years, differences between EPA and DOE concerning standards and acceptable risks for cleanups at DOE sites have contributed to regulatory delays and higher regulatory and cleanup costs while raising public questions about what cleanup levels are appropriate. See Nuclear Cleanup: Completion of Standards and Effectiveness of Land-Use Planning Are Uncertain (GAO/RCED-94-144, Aug. 26, 1994).



ED_002751_00006820-00023

For example, in individual situations at NRC-licensed sites, EPA has indicated that it might not view cleanups performed to NRC's standards as adequately protective under its Superfund guidance. EPA considers such potentially conflicting situations to be exceptions, not the rule. EPA raised the matter of the standards' adequacy twice in 1999 in connection with nuclear power plants in Maine and Connecticut where the decommissioning process is under way, and again in connection with the West Valley, New York, nuclear site, a DOE-operated facility where NRC has a legislatively mandated regulatory role. In such situations, the licensee may construe EPA's involvement as a warning that EPA could reevaluate the adequacy of a cleanup that has met NRC's requirements. In the New England cases, the licensee has thus far responded to the prospect of dual regulation by proceeding with its decommissioning plans, assuming that it will be able to comply with both agencies' standards.[29] In the West Valley case, it remains to be seen whether NRC's or EPA's approach will finally be chosen for the site.

Our 1994 report found that U.S. radiation standards reflected a lack of federal agency consensus on acceptable radiation risk to the public, particularly between EPA and NRC. We recommended that the two agencies take the lead in pursuing interagency consensus on acceptable radiation risks to the public. In succeeding years, EPA and NRC have attempted to resolve their conflict over cleanup standards by means of a memorandum of understanding that would clarify their potentially conflicting, dual regulation of NRC-licensed sites. In August 1999, the House Appropriations Committee strongly encouraged the two agencies to develop such a memorandum and directed them to report to the Congress by May 1, 2000, on the status of their efforts to do so.

In early May 2000, EPA and NRC informed the Committee by separate letters that they are developing such a memorandum, although a jointly drafted version of the memorandum does not yet exist. To date, EPA officials see such a memorandum as providing an outline of consultation procedures for EPA and NRC to use during NRC's decommissioning process when NRC requests EPA's assistance. It is unclear whether the memorandum will consider whether EPA should retain its authority to conduct a Superfund evaluation of an NRC-licensed or -decommissioned

[29]The licensee has stated that it can meet more stringent standards of 10 millirem a year, plus extra groundwater protection to the equivalent of 4 millirem a year, as imposed by the state of Maine.



ED_002751_00006820-00024

facility when a stakeholder requests such an evaluation. EPA believes it should retain this authority and has provided guidance to its regional offices on how to proceed when a stakeholder asks for an evaluation. According to this guidance, EPA believes that at the vast majority of NRC-licensed sites, cleanups that meet NRC's standards will also meet Superfund standards. An NRC draft version of the memorandum assumes that EPA will defer to NRC's radiological cleanup and decommissioning standards and regulations and will exempt most NRC-regulated sites from the application of the Safe Drinking Water Act and Superfund. NRC's version reflects the Commission's view that clearly delineated jurisdictions for the two agencies are needed.

## Costs Vary to Comply With Different Radiation Standards

Long-term costs related to complying with current and prospective U.S. radiation standards have generally not been comprehensively estimated, but these costs will be immense, likely in the hundreds of billions of dollars.[30] The potential size of these costs is reflected in DOE's long-term funding estimates for high-level waste disposal and nuclear cleanup projects. These estimates total more than $200 billion over many decades and could increase, according to DOE. In addition, DOE's, NRC's, and EPA's analyses of individual nuclear sites' cleanup options show that site-specific compliance costs can vary significantly depending on the restrictiveness of the standards. As might be expected, the analyses show that compliance with more restrictive standards—for example, exposure limits of a few millirem a year—costs considerably more than compliance with less restrictive standards—for example, limits of 100 millirem a year. Site-specific DOE analyses estimate multimillion-dollar cost differences between less restrictive and more restrictive protection levels, in some cases. These analyses further show faster rising costs to achieve the most restrictive protection levels.

[30]Annual costs and benefits of environmental regulations have been estimated to total many billions of dollars annually. For example, see R. Hahn, and J. Hird, "The Costs and Benefits of Regulations," Yale Journal on Regulation, vol. 8 (1991), pp. 233-78.



ED_002751_00006820-00025

## Costs of Implementing High-Level Waste Standards

To comply with high-level waste standards, DOE has projected multibillion dollar costs, whether or not the Yucca Mountain repository is developed. Radiation protection standards for Yucca Mountain have not been finalized,[31] but DOE has estimated funding of over $43 billion (in 1998 dollars) for the total repository system to 2116, in large part to help ensure that the public is protected from exposure to the waste stored there. According to DOE's latest estimates, long-term funding for the repository could go over $55 billion. Alternatively, if the repository is not built, DOE has estimated expenditures of about $52 billion to $57 billion to store high-level waste for 100 years at existing sites around the country. From the enactment of the Nuclear Waste Policy Act of 1982 through fiscal year 1998, DOE spent about $7 billion (in 1998 dollars) for its repository program.[32]

EPA, NRC, and DOE have not estimated the total difference in compliance costs under the conflicting standards proposed by EPA and NRC for Yucca Mountain. DOE officials said that most of the projected increases in the repository's costs can be associated with design changes resulting from the combination of EPA's proposed groundwater standards, the need to provide the level of confidence in the repository's performance required for a rigorous NRC licensing process,[33] and the influence of external oversight advisory bodies and peer review panels. DOE estimated that cost increases have totaled over $10 billion since 1993 to achieve added confidence that restrictive performance and radiation protection requirements can be met over thousands of years. For example, in 1993 a repository-performance-related increase of $7 billion (in 1999 dollars) came from a design change involving the use of more robust, cylindrical waste containers. Furthermore, DOE is considering an additional cost of $3.7 billion (in 1999 dollars) for water-diverting titanium drip shields (over the waste

[31]DOE officials said that since the 1990s, they have been designing the repository to more than meet prospective radiation standards that EPA and NRC might issue.

[32] At another nuclear waste disposal facility that is already in operation, the Waste Isolation Pilot Project, where EPA's transuranic waste disposal standards are operative, DOE projects funding to 2070 at $7.7 billion. In addition, state compacts and unaffiliated states have to date incurred almost $600 million in costs for planning and developing potential low-level waste disposal sites, although no sites have been built. See *Low Level Radioactive Wastes: States Are Not Developing Disposal Facilities* (GAO/RCED-99-238, Sept. 17, 1999).

[33]According to DOE and EPA, NRC's proposed "reasonable assurance" performance objective for the repository may be more stringent and costly to implement than the "reasonable expectation" compliance objective in EPA's proposed standards. NRC disagreed that this would necessarily be the case.



ED_002751_00006820-00026

containers) intended to protect the repository from potential water incursion, as well as to meet EPA's proposed groundwater protection requirements in a rigorous NRC licensing process. Further design enhancements to achieve a cooler repository, which would keep temperatures in the repository below the boiling point of water, as favored by the Nuclear Waste Technical Review Board, could add about $2 billion more to costs. According to DOE and NRC officials, the latest design is essentially an attempt to achieve a virtually "no radioactive release" facility at Yucca Mountain. These officials maintain that such a design may not be needed to implement less restrictive standards such as 15-, 25-, or 100-millirem-a-year all-pathway exposure limits.

## Costs of Implementing Nuclear Cleanup and Decommissioning Standards

Although comprehensive data on the costs of complying with nuclear site cleanup and decommissioning standards were unavailable, these costs could be immense in the long term. For example, complying with EPA Superfund cleanup and other environmental requirements may cost DOE several billion dollars annually, judging from the fact that the agency's fiscal year 1999 appropriation for the overall environmental management and cleanup of its nuclear facilities was about $5.8 billion. The agency's compliance activities could cost hundreds of billions of dollars and could extend for decades into the future, according to long-term funding estimates for environmental cleanup projects. The agency has projected funding for environmental cleanup at its nuclear sites from fiscal year 2000 through fiscal year 2070 to be anywhere from about $151 billion to $195 billion (in 1999 dollars). DOE spent about $52 billion for cleanup from fiscal year 1989 through fiscal year 1999. The overall bill for DOE's nuclear cleanup is uncertain and could go higher. According to DOE, the future costs of many of its cleanup programs are difficult to quantify because many projects are still in the planning stage. Moreover, as we noted in 1999, the data on some sites may not be reliable, in part because many field sites based their cost estimates on assumed cleanup levels that have not been finalized.[34] In addition, the operators of NRC-licensed nuclear facilities, including over 100 power plants, may spend over $38 billion for

[34]See *Nuclear Waste: DOE's Accelerated Cleanup Strategy Has Benefits but Faces Uncertainties* (GAO/RCED-99-129, Apr. 30, 1999). According to DOE, about 85-90 percent of its environmental management budget is directed toward ensuring compliance with the large number of legally enforceable cleanup and compliance agreements in place at major sites around the country. Such compliance involves not only EPA requirements, such as Superfund, but also any applicable state requirements, as well as DOE's own radiation protection orders.



ED_002751_00006820-00027

decommissioning in coming decades, according to the Nuclear Energy Institute.

Even though EPA, NRC, and DOE generally did not have estimates for all U.S. nuclear sites of the costs of complying with different cleanup standards to achieve different protection levels,[35] officials from these agencies said that achieving more restrictive protection levels, especially the most restrictive levels—in the range below 100 millirem a year—can be considerably more expensive. To support their statements, they cited various generic and site-specific cost analyses conducted by DOE, NRC, and EPA. Our examination of these cost analyses generally confirmed higher estimated costs to comply with more restrictive cleanup levels for contaminated soil, as might be expected. Conversely, cost estimates were considerably less to comply with less restrictive soil cleanup levels. For example, analyses comparing the costs of achieving EPA's and NRC's conflicting all-pathway cleanup levels—15 millirem a year and 25 millirem a year, respectively—show cost differences in the millions of dollars for some sites—and even greater cost differences to achieve cleanup levels below 10 millirem a year. Analyses also show potential multimillion-dollar cost differences between the 15 to 25 millirem-a-year range and the less restrictive 100-millirem-a-year level.

Among the analyses we examined were a generic analysis by NRC to support its decommissioning standards and numerous site-specific cost analyses done by DOE in the course of analyzing cleanup options for its nuclear weapons complex. The estimated costs of meeting different soil cleanup levels for selected sites are summarized in table 1 and discussed in more detail in appendix V.

[35]An exception is a preliminary regulatory analysis done by EPA in 1996 to support its proposed cleanup standards. The analysis showed incremental cost differences in the low billions of dollars to meet various cleanup levels below 100 millirem a year. See app V.



ED_002751_00006820-00028

**Table 1: Estimated Costs to Achieve Different Soil Cleanup Levels at Selected DOE Sites and Generic NRC-Licensed Sites**

Dollars in millions

| Agency/site/ analysis date | Cost of 100 millirem a year | Cost of 25 millirem a year | Cost of 15 millirem a year | Cost of less than 10 millirem a year |
|---|---|---|---|---|
| DOE/Nevada Test Site and test ranges/1995 | 35 | 131 | 240 | 1,003[a] |
| DOE/Brookhaven Laboratory waste facility/1998 | 15.9 | 24.4 | 28.2 | 64.5[b] |
| NRC-licensed power plant[c] /1997 | 0.17 | 0.31 | 0.41 | 1.44[d] |
| NRC-licensed metal extraction facility[c]/1997 | 5.30 | 6.21 | 7.33 | 13.86[d] |

Note: Totals do not represent overall estimates of cleanup costs, which may include costs for activities other than soil cleanup, including the decontamination and removal of equipment and structures, as well as liquid waste treatment.

[a]5 millirem a year.

[b]1 millirem a year. Totals are present values.

[c]Generic site.

[d]3 millirem a year.

Source: GAO's presentation of data from DOE and NRC.

As shown in table 1, for the listed sites, the estimated costs to achieve different soil cleanup levels vary, from hundreds of thousands of dollars in some cases to hundreds of million dollars in other cases. The cleanup costs also accelerate faster to achieve the most restrictive levels. For example, for the Nevada Test Site, from a 100-millirem-a-year baseline, the costs increase over three times and over six times to achieve the 25-millirem-a-year and 15-millirem-a-year levels, respectively, but over 28 times to achieve the 5-millirem-a-year level. Similarly, for the Brookhaven facility, from a 100-millirem-a-year baseline, the costs increase about 53 percent to achieve the 25-millirem-a-year level, about 77 percent to achieve the 15-millirem-a-year level, but over 300 percent to achieve the 1-millirem-a-year level. DOE and NRC officials said the large cost variations for different sites reflected site-specific factors, including the ratio of soil and building contamination, exposure and land-use scenarios, and waste disposal options. Officials said cost factors include not only the degree of on-site



ED_002751_00006820-00029

remediation, but also soil sampling and analysis to demonstrate compliance with standards, as well as procedural and other costs.[36]

Fewer analyses of the costs of complying with EPA's extra groundwater protection approach for nuclear cleanups were available. However, DOE's groundwater remediation analyses for aquifers at the Idaho National Engineering and Environmental Laboratory and at the Brookhaven National Laboratory showed that the additional costs of achieving drinking water standards at these sites could approach several hundred million dollars and a few million dollars, respectively, depending on the remediation option chosen. (See app. V.)

## Conclusions

Although conclusive scientific evidence of the effects of low-level radiation is lacking and may not soon be found, U.S. regulators still have the challenge of developing radiation standards that represent their best estimates of acceptable radiation risks to the public. In this regard, as a national decision on high-level-waste disposal at Yucca Mountain approaches, and as EPA and NRC both continue to administer the cleanup and decommissioning of nuclear sites, it is important that the two agencies agree on protection approaches and policies for these regulatory applications. However, it does not appear that EPA and NRC will readily agree on appropriate groundwater protection approaches for Yucca Mountain. Also, EPA and NRC have been working on a memorandum of understanding since before August 1999, when the House Appropriations Committee encouraged them to clarify their conflicting regulatory roles related to nuclear facility cleanup and decommissioning, with little progress. Looking back, we note that they have not successfully addressed this matter since at least 1994, when we recommended that they pursue consensus on acceptable radiation risks to the public. Given the agencies' historical differences and lack of recent progress, without congressional intervention, they may not resolve their differences.

It is of note that EPA and NRC, while disagreeing over appropriate public protection levels, are both regulating at levels where the harm of radiation and the health benefits of radiation standards may not be clearly

[36]These analyses do not consider overall site cleanup costs, which may include many factors, such as the costs of decontaminating and removing structures and treating liquid waste. The analyses often estimated hypothetical cancer deaths averted from meeting various protection levels.



ED_002751_00006820-00030

demonstrable. Regulating at these levels, well below the range where radiation effects have been conclusively verified, is essentially a policy judgment. Such an approach may arguably be prudent, in accordance with regulatory use of the linear model, which both agencies endorse. However, it will also be expensive, because compliance costs accelerate to achieve the lowest exposure levels, as our work confirms. The potential acceptable risks, health benefits, and costs of EPA's and NRC's differing regulatory approaches will be of interest to the Congress as it continues to focus on nuclear health and safety issues of national importance, such as the proposed Yucca Mountain repository and the cleanup and decommissioning of federal and commercial nuclear sites. These risks, benefits, and costs will also affect the public's belief in and acceptance of any resolution of their conflicting viewpoints that the two agencies may achieve.

## Matters for Congressional Consideration

The congressional committees of jurisdiction may wish to reconcile EPA's and NRC's policy differences on groundwater protection for Yucca Mountain. Also, in connection with the two agencies' efforts to complete a memorandum of understanding relating to the cleanup and decommissioning of nuclear sites, these Committees may wish to clarify the agencies' regulatory responsibilities.

## Agency Comments

We provided NRC, DOE, and EPA with a draft of this report for their review and comment. NRC found the report to be fundamentally sound and said it should help the Congress understand the long-standing differences between EPA and NRC. NRC supported our conclusions that federal agencies should agree on decommissioning and high-level waste policies and approaches to ensure consistent standards and public protection. DOE found the report to be factual and balanced. EPA disagreed with the report, in separate letters from its Office of Radiation and Indoor Air and Office of Emergency and Remedial Response. The Director, Office of Radiation and Indoor Air, said EPA interprets the information presented in our report differently, and as a result, EPA disagrees with the report's conclusions. The Director, Office of Emergency and Remedial Response, said, among other comments, that the report inaccurately portrays EPA and NRC as making little progress in their negotiations on a memorandum of understanding to clarify the two agencies' regulatory roles and responsibilities related to the cleanup and decommissioning of nuclear facilities. EPA mentioned recent and continuing efforts by the two agencies



ED_002751_00006820-00031

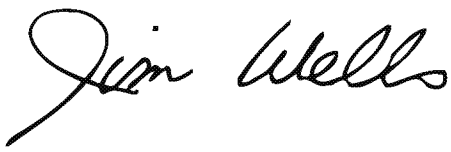
to better clarify their respective regulatory roles through such a memorandum. While recognizing these recent initiatives, we note that since as long ago as 1992, the two agencies have been unsuccessful in addressing this matter, and on this basis we still question whether the two agencies' most recent initiatives will resolve their differences without congressional intervention.

NRC, DOE, and EPA provided technical clarifications to the draft report, which we incorporated into the final report where appropriate. EPA's, NRC's, and DOE's comments and our evaluation of them are included in appendixes VI, VII, and VIII.

As arranged with your office, unless you publicly announce its contents earlier, we plan no further distribution of this report until 20 days after the date of this letter. At that time, we will send copies to the Honorable Carol Browner, Administrator, Environmental Protection Agency; the Honorable Richard Meserve, Chairman, Nuclear Regulatory Commission; and the Honorable Bill Richardson, Secretary of Energy. We will also make copies available to others upon request.

If you have any questions about this report, please contact me or (Ms.) Gary L. Jones on (202) 512-3841. Key contributors to this assignment were Duane G. Fitzgerald and Dave Brack.

Sincerely yours,



Jim Wells, Director, Energy, Resources,
and Science Issues



ED_002751_00006820-00032

ED_002751_00006820-00033

# Scope and Methodology

To conduct our review of U.S. radiation standards, we obtained testimonial and written documentation from many dozen recognized scientists in the field of radiation research and radiation protection, including both active research scientists and representatives on national and international radiation protection committees; officials of federal agencies principally responsible for regulating public radiation protection and conducting scientific research into the health effects of low-level radiation, including EPA, NRC, DOE, the Department of Defense, and the Department of Health and Human Services; state radiation protection officials and the Conference of Radiation Control Program Directors; officials of radiation protection organizations, such as the National Council on Radiation Protection and Measurements, the National Academy of Sciences, and the International Commission on Radiological Protection; environmental and nuclear industry representatives; and individual radiation researchers in government, industry, and academia.

To examine the scientific basis of U.S. radiation standards, we obtained expert views representing various viewpoints in the controversy over low-level radiation and the linear model. In addition, we hired an expert consultant to help synthesize data and draw conclusions relating to the status of studies correlating worldwide natural background radiation levels to cancer rates, as well as their possible implications for setting radiation standards. The consultant, Dr. Thomas Gesell, Professor of Health Physics, Idaho State University, is a recognized expert in environmental radiation. (Results based on the consultant's work, representing GAO's views, are presented in detail in app. IV.) Furthermore, we asked several experts in the radiation protection field to informally review and comment on the accuracy of a draft version of our report, and we incorporated their suggested changes where appropriate.

To examine whether federal agencies have come closer to agreeing on radiation standards since we reported on this matter in 1994, we obtained views and documentation from agency officials, the Interagency Steering Committee on Radiation Standards, and the Conference of Radiation Control Program Directors. We examined various federal and state radiation standards, as well as the regulatory and compliance activities of various federal agencies. However, we mainly focused on prominent current instances of disagreement between EPA and NRC, over radiation protection standards for high-level waste disposal and for the cleanup and decommissioning of nuclear facilities.



ED_002751_00006820-00034

To examine the costs of radiation standards, although comprehensive estimates of these costs were unavailable, we obtained indications of these costs through available agency radiation-related cost and funding data. To examine the costs of different standards and protection levels, although comprehensive estimates of these differences were unavailable, we obtained indications of these costs through examining generic and site-specific agency cost analyses. We especially looked for analyses that showed estimated costs to achieve different radiation exposure levels, and we took steps to reasonably ensure that the analyses represented the best available data. Specifically, we obtained (1) analyses agencies considered representative of the best available data, (2) information on internal and external peer review and other quality controls steps that agencies may have taken in connection with the analyses, and (3) agency officials' views on any data limitations in the analyses.

We performed our review between July 1999 and June 2000 in accordance with generally accepted auditing standards.



ED_002751_00006820-00035

# Major U.S. Radiation Standards

| Standard/agency | Numerical limit |
|---|---|
| General standards | |
| General public/NRC (10 C.F.R. 20) | 100 millirem/year |
| Source-specific standards | |
| Uranium mill tailings/EPA, NRC (40 C.F.R. 192; 10 C.F.R. 40, App. A) | Radium 226, 228: 5 picocuries/gram surface,<br>15 picocuries/gram subsurface<br>Radon 222: 20 picocuries/square-meter-second[a] |
| High-level waste operations/NRC (10 C.F.R. 60) | 100 millirem/year |
| Spent fuel, high-level waste, transuranic waste disposal/EPA (10 C.F.R. 191) | All pathway: 15 millirem/year<br>Groundwater 4 millirem/year[b] |
| Yucca Mountain high-level waste (proposed)/EPA (64 Fed. Reg. 46976) | All pathway: 15 millirem/year<br>Groundwater 4 millirem/year[b] |
| Yucca Mountain high-level waste (proposed)/NRC (64 Fed. Reg. 8640) | 25 millirem/year all pathway |
| Low-level waste/NRC (10 C.F.R. 61) | 25 millirem/year |
| Drinking water/EPA (40 C.F.R. 141) | Radium: 5 picocuries/liter<br>Gross alpha: 5 picocuries/liter<br>Beta/photon: 4 millirem/year[b] |
| Uranium fuel cycle/EPA (40 C.F.R. 190) | 25 millirem/year |
| Superfund cleanup/EPA (40 C.F.R. 300) | Risk range goals: 1 in 10,000 to 1 in 1 million[c] |
| Decommissioning/NRC (10 C.F.R. 20) | 25 millirem/year |
| **Occupational standards** | |
| Occupational Safety and Health Administration, NRC, DOE (29 C.F.R. 1910; 10 C.F.R. 20; 10 C.F.R. 835) | 5,000 millirem/year |

[a]A picocurie is a trillionth of a curie, which is a commonly used unit of measurement of the activity of radiation.

[b]Radioactivity from human-made radionuclides in community drinking water systems.

[c]Lifetime risk of an individual's getting cancer.

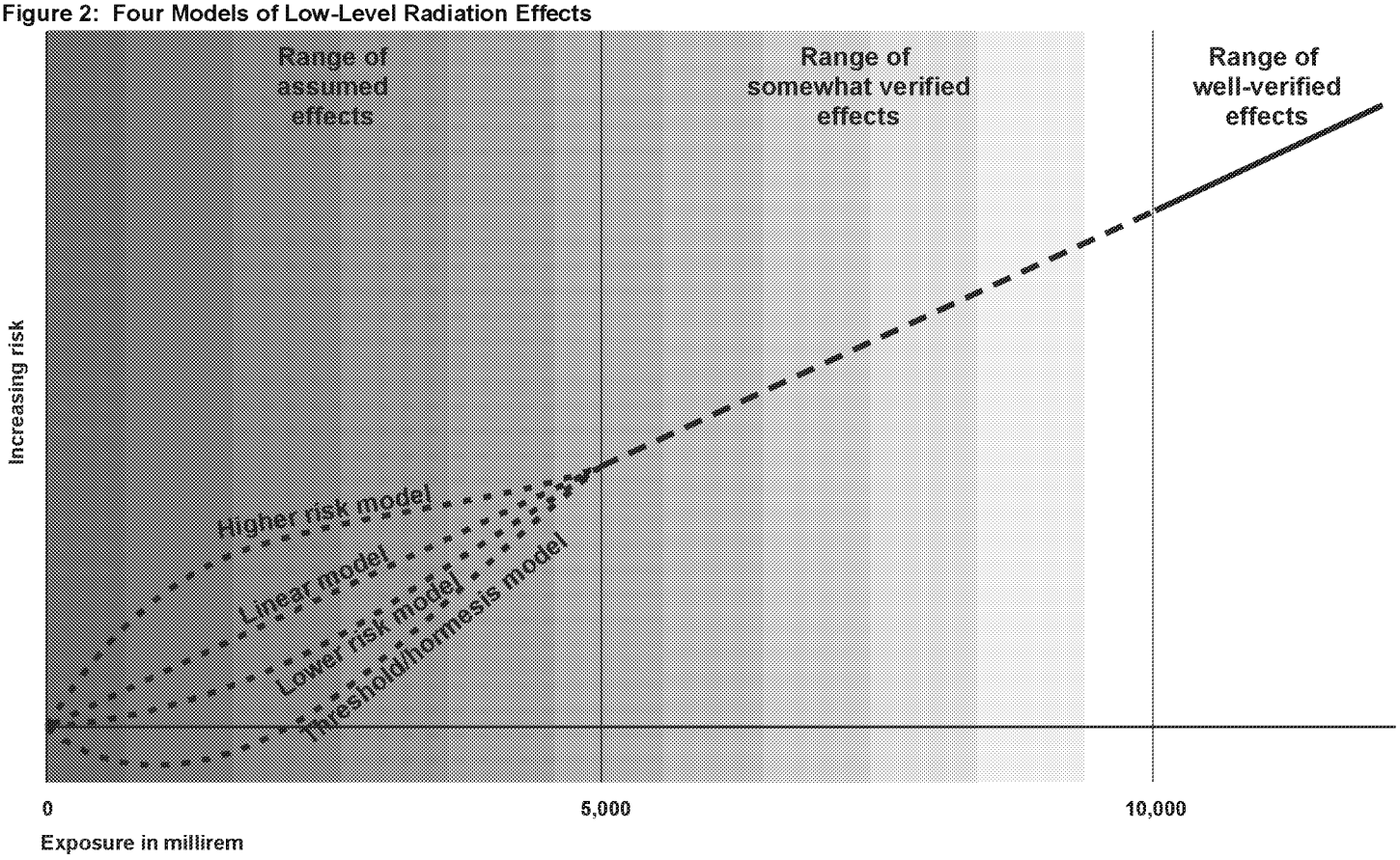


ED_002751_00006820-00036

# Examples of Different Models of Low-Level Radiation Effects

Figure 2 shows different models of low-level radiation effects that could fit the available research data. The linear model is used and endorsed by regulators and radiation protection organizations. The threshold model is preferred by those who interpret the data as showing that there are no effects below a certain exposure level. The higher-risk model is preferred by those who interpret the data as showing higher risks than the linear model. The lower-risk model is preferred by those who interpret the data as showing lower risks than the linear model.

**Figure 2: Four Models of Low-Level Radiation Effects**






ED_002751_00006820-00037

# Overview of Epidemiological Research on Low-Level Radiation Effects

Epidemiological research has been part of the scientific basis for the linear model and radiation standards. However, epidemiology may not soon fully verify or disprove low-level radiation effects. Specific epidemiological research correlating natural background levels in the United States and around the world with cancer rates has been generally inconclusive, showing mixed results. Much of this research has used methodologies that have been widely considered too limited for the research to be influential in setting radiation standards.

Several U.S. agencies are involved in epidemiological research on low-level radiation effects, including the Department of Energy (DOE), the Department of Health and Human Services (HHS), and the Department of Defense (DOD). In fiscal year 1999, about $41 million in DOE funding went for epidemiological research, including about $24 million provided to HHS for epidemiological and environmental research at DOE's nuclear sites, under a 1994 memorandum of understanding that established independent management of such research. (In comparison, in fiscal year 1999, about $12 million for radiobiological research was funded within DOE's Office of Biological and Environmental Research, and DOD provided an estimated $11 million for radiobiological research at its Armed Forces Radiobiology Research Institute.)

## Japanese and Worker Studies

Epidemiological results have been a key basis for the linear model, including the study of over 85,000 Japanese survivors of the Hiroshima and Nagasaki bomb blasts. The United States has for many years participated in this study, conducted by the international Radiation Effects Research Foundation, with funding by DOE—$14 million in fiscal year 1999—through the National Academy of Sciences. The still-continuing study has helped to establish the effects of radiation at levels above 10,000 millirem, for which the data show a relationship between exposures and health effects that is generally consistent with a linear model. With a considerable degree of inherent uncertainty, scientists have extrapolated this relationship to the low-level radiation range as well. Based in large part on the Japanese data, major radiation protection organizations have endorsed the assumption of a linear dose-response relationship at far lower public exposure levels, down to those commonly regulated—100 millirem a year and below.

Some scientists have questioned the foundation's work, asserting that the study understates radiation risk because it necessarily focuses on bomb survivors, who likely were the healthiest of the blast victims. Others assert



ED_002751_00006820-00038

that the important neutron component of the estimated Hiroshima dose is questionable, calling into doubt the overall Hiroshima-Nagasaki dose estimates dating from 1986. Recognizing that the Japanese data have historically been central to radiation risk estimation and that credible Hiroshima and Nagasaki dose estimates are needed, DOE and the National Academy of Sciences are conducting a reassessment of the Hiroshima neutron doses. Results are expected in late 2000. According to DOE, it is likely that new Radiation Effects Research Foundation dose estimates for Hiroshima and Nagasaki will be derived and that they will be issued in 2001.

In addition, there have been many epidemiological studies of U.S. and foreign nuclear workers, medical patients, miners, and others exposed to various levels of low-level radiation. For example, historically DOE has funded over 40 epidemiological studies of radiation effects on workers at sites in the U.S. nuclear weapons complex. According to DOE, the results have shown elevated cancer levels from chronic exposure at some sites, among the most highly exposed workers, although the results have been inconsistent and, looking complex-wide, DOE has not found a clear pattern of excess risk for any specific cancer type. In general, epidemiological studies of workers and other groups have the limitation of attempting to follow research populations that may be too small to give statistically powerful or conclusive results about very low radiation doses, and sometimes the studies do not follow populations over a long enough period of time, according to researchers and agency officials.

## Studies Correlating Natural Background Radiation With Cancer Rates

Epidemiological studies have been involved in the controversy over low-level radiation effects because many such studies have attempted to statistically correlate natural background radiation levels (principally radon) in the United States and around the world with local cancer rates. A premise in the controversy is that in places with higher background radiation levels, the studies should show elevated cancer rates if there is a linear relationship between low-level exposures and health risks. Some of the studies have focused specifically on areas with the highest natural background radiation levels. In some places, these levels are four or five times as high as average U.S. levels. Two types of studies have been conducted. One type relates regional rates of disease, often obtained from published vital statistics, to measures of regional radiation levels. These are called ecologic studies. The other type obtains disease data by direct interviews of individuals or their representatives and by direct measurement of radiation exposures. These are called analytic studies.



ED_002751_00006820-00039

Analytic studies can be prospective, following populations and current exposures for future outcomes, or retrospective, comparing current outcomes to past exposures.

For this review, we hired a consultant, Dr. Thomas Gesell, Professor of Health Physics, Idaho State University, a recognized expert in the field of environmental radiation, to identify and summarize worldwide ecologic and analytic studies of natural background radiation or radon. Through his work, we found that many ecologic and analytic studies have been done in the United States, Europe, Asia, and South America. Some focused mainly on radon effects, and others focused more broadly on overall natural background radiation effects. The results of such studies differ and are inconclusive overall. Most showed no evidence of elevated cancer risk, but a minority did show slightly elevated cancer risks. Taken together, the studies may suggest that low-level radiation effects are either very small, or nonexistent. Scientists have disputed the importance of such studies in determining low-level radiation effects. A factor in the dispute is the methodological difficulty of performing meaningful epidemiological studies of cancer rates in populations exposed to chronic low-level radiation doses. In many cases the population being studied is limited in size, and the cancer effects being pursued are small, making them difficult to detect among all cancers in the population.

In most places on earth, natural background radiation (excluding radon) varies within about a factor of four, and cosmic radiation varies by about a factor of two in the elevations where most of the world's population lives. Average world natural background radiation levels are about 240 millirem a year (including radon), and about 300 millirem a year in the United States. Particularly high concentrations of natural background radiation have been reported in Brazil, India, China, and Iran. For example, there are areas of elevated levels in Brazil, one along the coast (Guarapari) and another in the interior (state of Minas Gerias); in the Kerala area, India; in Yangjiang County, southwest Guangdong Province, China; and in Ramsar, Caspian coast, Iran. In some of these areas, mean annual doses can be more than double average U.S. levels, and hot spots into several thousand millirem a year have been reported. In the United States, natural background levels are over three times higher in the Rocky Mountains than along the Gulf Coast.

With the help of our expert consultant, we examined 82 ecologic and analytic studies of natural background radiation or radon, in the United States and around the world. Of these studies, 45 were directly radon



ED_002751_00006820-00040

related. The studies examined a variety of different types of cancer, and some examined cancer effects on children, while others examined genetic effects. Results of the studies varied, and we did not independently assess their quality. Some reported statistically significant results—elevated cancer rates, no elevation in rates, or a negative correlation—and others reported inconclusive results. (Some lacked basic information for assessing their quality.) Of 67 radon-related cancer studies, 22 reported results indicating a statistically significant correlation between natural background radiation or radon and cancer rates, while 45 found no such correlation (including 8 that found a negative correlation), and 4 were inconclusive. Others reported statistically significant chromosomal aberrations in subjects, but not cancer correlations.

In 1999, the National Academy of Sciences issued a report on the health effects of radon exposure, called BEIR VI. Of 39 studies examined in the report, including 19 ecologic studies, 17 studies reported a positive correlation between radon and lung cancer, and 15 reported no correlation. Three reported a negative correlation, including a 1995 ecologic study by Bernard Cohen, University of Pittsburgh, of radiation-cancer correlations in 1,601 U.S. counties. The study found a strong tendency for lung cancer rates to decrease with increasing radon exposures, in sharp contrast to the increase expected from the linear model. The study and follow-up analysis took steps to test for over 500 potential confounding factors, including smoking and other lifestyle factors. The author found no potential explanation for the discrepancy other than failure of the linear model. Some critics of the study consider it to be carefully and thoroughly done but believe that it lacks adequate data to control for smoking or other factors. Many epidemiologists consider all ecologic studies to be methodologically inferior to analytic case control studies because the former compile average statistics, not individual statistics. Some analytic case control studies have contradicted the Cohen study, including a 1997 meta-analysis (study of studies) involving eight individual analytic studies of radon and lung cancer. The meta-analysis found a small positive correlation between indoor radon levels and lung cancer. However, the meta-analysis also found considerable variance in the eight studies' results, and specific lifestyle or socioeconomic confounding factors that would directly negate the Cohen study's results have not been isolated, although various theories have been put forward.



ED_002751_00006820-00041

# Costs of Different Radiation Standards

We examined numerous EPA, NRC, and DOE analyses of different nuclear cleanup options and costs. The analyses generally confirmed that, as might be expected, compliance costs varied to achieve different radiation protection levels and accelerated to achieve more restrictive levels. The analyses were done between 1991 and 1999, and they estimated costs under varying scenarios to achieve different dose, risk, and contamination levels.[1] In particular, we examined several site-specific DOE nuclear cleanup studies; an NRC environmental impact study of four types of generic NRC-regulated facilities, performed to support NRC's decommissioning standard; and a draft EPA regulatory impact analysis of the potential nationwide costs (at 16 generic types of sites) of EPA's proposed comprehensive cleanup standards. Selected analyses that showed cost variations in relation to achieving different millirem levels are discussed below.

## Costs of Cleaning Up to Different Protection Levels

Our examination of DOE's and NRC's analyses showed potential site-specific cost differences of millions of dollars, in some cases, between cleaning up radioactively contaminated soil to 15 millirem a year and cleaning it up to 25 millirem a year, under various scenarios. (These analyses do not represent estimates of overall site cleanup costs, which may include factors in addition to soil cleanup, including remediation activities such as the decontamination and removal of contaminated equipment and structures and liquid waste treatment.) EPA's analysis showed potential nationwide incremental costs in the low billion dollars to achieve more restrictive cleanup levels.[2] Major analyses that showed cost variations in the range of 100 millirem a year and below are shown in table 2.

[1]Often, in addition to costs, the analyses estimated doses and cancer deaths averted from meeting various protection levels, using the linear model.

[2]EPA quantified soil cleanup costs in the draft analysis. According to DOE's comments on the analysis, EPA may have greatly underestimated the potential costs of implementing EPA's drinking water standards for groundwater at DOE sites.



ED_002751_00006820-00042

**Table 2: Potential Costs to Achieve Different Soil Cleanup Levels—DOE's, NRC's, and EPA's Analyses**

Dollars in millions

| Agency/site/analysis date | Estimated soil cleanup cost | | | |
|---|---|---|---|---|
| | 100-millirem-a-year level | 25-millirem-a-year level | 15-millirem-a-year level | Less than 10-millirem-a-year level |
| DOE | | | | |
| Hanford process waste areas, 1994[a] | b | 14 | 19 | 59[c] |
| Nevada Test Site and test ranges, 1995[d] | 35 | 131 | 240 | 1,003[e] |
| Weldon Spring, 1991[f] | b | 0.58 | 1.4[g] | 2.0[h] |
| Brookhaven waste facility, 1998[i] | 15.9 | 24.4 | 28.2 | 64.5[j] |
| NRC[k] | | | | |
| Generic nuclear power plant, 1997 | 0.17 | 0.31 | 0.41 | 1.44[c] |
| Generic fuel fabrication facility, 1997 | 2.89 | 6.35 | 7.83 | 13.56[c] |
| Generic metal extraction facility, 1997 | 5.30 | 6.21 | 7.33 | 13.86[c] |
| Generic sealed source facility, 1997 | 0.08 | 0.26 | 0.35 | 0.64[c] |
| EPA | | | | |
| Generic nationwide sites, 1996[l] | m | 1,000 | 1,500 | 3,200[c] |

[a]The analysis was part of a feasibility study for a Superfund cleanup of ponds, trenches, and burial grounds in Area 300, where uranium and other wastes from processing nuclear fuel for Hanford's production reactors were disposed of over decades. Under an industrial scenario, the analysis considered five cleanup options. The totals shown are for the selected cleanup and disposal option and are present values.

[b]Cost not calculated for this level.

[c]3 millirem a year.

[d]At the site and test ranges (Nellis and Tonapah), plutonium contaminates surface soils over an estimated 90,000 hectares (at levels above 10 picocuries per gram). The contamination resulted from atmospheric nuclear tests, as well as safety tests that subjected nuclear devices to conventional explosives. The analysis was conducted separately from the Superfund process, as a cost-risk-benefit case study to evaluate a range of cleanup alternatives, using an active institutional controls scenario to limit costs. An integration model was used to estimate individual risks, population risks, costs (cleanup costs, costs of worker fatalities), and benefits (including reduced future on-site cancer fatalities). The totals assume on-site disposal for the Tonapah range waste.

[e]5 millirem a year.

[f]The analysis supported the Superfund process for the site, in Missouri, where uranium and thorium ore were processed from 1957 until 1966, contaminating buildings and soil. Under an on-site farmer scenario, alternative uranium soil cleanup levels were calculated. A 25-millirem-a-year cleanup target was selected, with an as low as reasonably achievable (ALARA) goal equivalent to 6.7 millirem a year.

[g]12 millirem a year.

[h]6.7 millirem a year.

[i]The facility historically processed, treated, and stored radioactive and hazardous waste. The analysis was conducted apart from the Superfund process, as an ALARA case study. Using an open space scenario, the analysis undertook risk optimization to determine the cost savings from the remedial action, the life-cycle costs for the remedial action, the value of the net dose avoided, and the value of



ED_002751_00006820-00043

other avoided risks and damages. In the net benefit-cost analysis, net costs resulted at all millirem-per-year levels. The totals shown represent present values.

[j]1 millirem a year.

[k]The four generic types of NRC-liensed facilities were included in a generic environmental impact statement supporting the issuance of the agency's decommissioning standard. The generic environmental impact statement included analyses of human health impacts, costs, and the cost-benefit of the regulatory action, under an unrestricted-use scenario. The totals shown reflect soil removal and survey costs, based on "real world" soil characterization estimates.

[l]The analysis was part of a regulatory impact analysis supporting EPA's prospective nuclear site cleanup standard. The analysis addressed incremental soil cleanup cost and health impact differences nationwide, between a base case (100 millirem a year, absent the proposed EPA standard) and the regulatory case (assuming promulgation of the EPA standard) for 16 types of reference sites, based on actual DOE, DOD, and NRC-licensed sites. Results were calculated for three scenarios—upper- and lower-bound scenarios and an intermediate scenario representing EPA's best estimate. The totals shown reflect the intermediate case, representing incremental soil cleanup costs below a 100-millirem-a-year baseline. The totals represent present values.

[m]The 100-millirem-a-year baseline.

As shown in table 2, for individual DOE and NRC-licensed sites, the estimated differences in compliance costs between the 15-millirem-a-year and the 25-millirem-a-year levels—reflecting EPA's and NRC's all-pathway standards, respectively—varied widely, from thousands of dollars to over $100 million. Similarly, the table shows widely varying cost differences between the 100-millirem-a-year level and lower levels. EPA's analysis estimated incremental compliance costs for multiple sites nationwide. As shown in the table, the analysis found cost differences of over a billion dollars between the 100-millirem-a-year level and lower levels.

The varied costs in table 2 reflect not only different protection levels but also different land-use scenarios and site characteristics, among other factors. For example, the 1995 analysis for the Hanford process waste areas used an industrial scenario, at a location with a variety of soil and structure components; the 1995 analysis for the Nevada test ranges used an active institutional controls scenario, at a large, soil dominated location; and NRC's 1997 analysis used unrestricted access scenarios, at generic industrial sites with substantial on-site structures. According to DOE analysts, scenarios involving on-site unrestricted, residential, or industrial

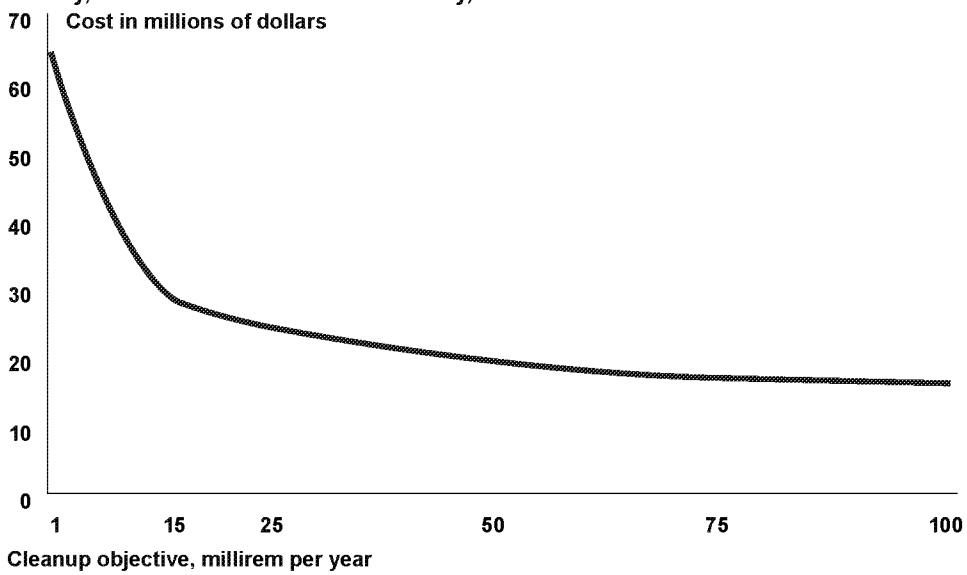


ED_002751_00006820-00044

use can result in much lower cleanup levels and higher cleanup costs than scenarios involving restricted or open-space use.[3]

The analyses also generally showed that cleanup costs accelerated to achieve the most restrictive protection levels. These accelerating costs can be shown graphically in the form of a cost-benefit curve, as depicted in figure 3, for the Brookhaven hazardous waste facility:

**Figure 3: Cleanup Costs as a Function of Cleanup Levels—Hazardous Waste Facility, Brookhaven National Laboratory, 1998**




As shown in figure 3, in the Brookhaven analysis, costs were a function of cleanup levels, increasing gradually, from right to left, from 100 millirem a year to 15 millirem a year, and accelerating from 15 millirem a year to 1 millirem a year. Conversely, rates of dose reduction (and potential

[3]For example, the choice of an open space scenario for the Rocky Flats facility in Colorado was a factor in the decision to apply a less restrictive plutonium cleanup level there than was required at the Nevada Test Site. See *DOE: Accelerated Cleanup of Rocky Flats—Status and Obstacles* (GAO/RCED-99-100, Apr. 30, 1999). The Rocky Flats plutonium cleanup level is being reconsidered in response to stakeholders' concerns, and a preliminary DOE cost estimate for a many times more restrictive cleanup level showed potential cleanup cost increases for Rocky Flats in the tens of millions of dollars.



ED_002751_00006820-00045

associated increased health benefits) decelerated at costs above $30 million. This relationship generally held for many DOE analyses we examined, including some that expressed cleanup levels in terms of risk and others that expressed cleanup levels in terms of concentration levels achieved.[4] According to DOE analysts, under the principle of reducing doses to levels as low as reasonably achievable (ALARA), there is a point or "elbow" on the cost-curve where an optimal balance between costs and cleanup level is chosen.

## Costs of Groundwater Cleanup

Agencies generally did not have overall estimates of the cost differences between achieving NRC's all-pathway 25-millirem-a-year limit for nuclear cleanups and achieving EPA's proposed extra groundwater protection requirements, based on the agency's more restrictive drinking water standards. However, available DOE and NRC analyses showed potential multibillion dollar cost differences per site to achieve EPA's standards. Both NRC and DOE expressed concern that the extra groundwater protection favored by EPA for nuclear sites could impose multimillion dollar additional costs annually at sites with groundwater contamination. NRC, in part, based its concern on an analysis done to support its decommissioning standard. This analysis showed that at a generic nuclear site with strontium 90 groundwater contamination, from a baseline of 25 millirem a year, incremental costs using "pump and treat" methods could be as high as $7 million to achieve a 3-millirem-a-year level (below the original 4 millirem-a-year drinking water standard, but above the level for strontium 90 using up-to-date dose estimation methods—0.07 millirem a year) and an additional $32 million to achieve natural background levels. ("Pump and treat" means that the water is pumped out of the ground, treated by various means, and discharged back into the ground.)

Site-specific DOE analyses also indicated incremental costs of many millions of dollars per site to meet drinking water standards through long-term pump and treat techniques. For example, a 1998 DOE analysis, issued in concert with EPA and the Idaho Department of Health and Welfare, showed options for cleaning up the Snake River Plain Aquifer underneath

[4]Other analyses included a draft 1999 analysis at two Nevada Test Site locations in the Tonapah test range; a 1999 analysis at the Energy Technology and Environmental Center, Santa Susana, California; a 1995 analysis at the Elza Gate, Tennessee, former waste storage site; and a 1994 analysis at the Ventron, Massachusetts, former uranium compounds processing facility.



ED_002751_00006820-00046

the spent fuel processing facility at the Idaho National Engineering and Environmental Laboratory. According to the analysis, the costs of using a pump and treat approach, if necessary to achieve the drinking water standard for a key radionuclide, Iodine 129, by 2095, could be anywhere from about $40 million to about $788 million depending on the aggressiveness of the approach taken.[5]

Also, a 1998 Brookhaven National Laboratory analysis of pump and treat options to clean up tritium and strontium 90 in the on-site groundwater showed that natural attenuation of the strontium 90 for 60 years or more might meet the drinking water standard for strontium 90 and cost less than a million dollars for monitoring activities. Alternatively, pump and treat methods might achieve the drinking water standards in 30 or more years, at costs of from $5.8 million to $6 million.

[5]According to a DOE-Idaho official, a December 1999 record of decision based on the analysis chose a less expensive aquifer dilution and monitoring approach.



ED_002751_00006820-00047

# Comments From the Environmental Protection Agency

Note: GAO comments supplementing those in the report text appear at the end of this letter.

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 13 2000

OFFICE OF
AIR AND RADIATION

Jim Wells, Director
Energy, Resources, and Sciences Issues
Resources, Community, and Economic Development Division
U. S. General Accounting Office
Washington, DC 20548

Dear Mr. Wells:

Thank you for the opportunity to provide comments on the General Accounting Office (GAO) Report, "Low-level Radiation Standards - Scientific Basis Inconclusive, and EPA and NRC Disagreement Continues." Our principal comments on the report can be divided into three areas - the use of the linear non-threshold (LNT) model for estimating the risk of radiogenic cancers; the Environmental Protection Agency's (EPA) groundwater protection strategy and its application in the proposed Yucca Mountain regulations; and, our efforts to develop a Memorandum of Understanding (MOU) with the Nuclear Regulatory Commission (NRC) on the clean-up of NRC-licensed sites. In all these areas, we interpret the information differently and as a result, we disagree with the report's conclusions.

Linear No-Threshold Dose Response Model

The first issue, that of whether the U.S. government should continue to use the LNT model, is a question that has received considerable attention in recent years. While there is some uncertainty associated with the risk estimates at low radiation exposures, the LNT is supported by all major consensus scientific organizations and is used by every national and international regulatory body as the basis for its radiation protection strategies. Until the evidence suggests otherwise, EPA is simply following the consensus of scientific organizations in continuing to use the LNT model to estimate risks.

See comment 1.

Several national and international workshops have been held to re-examine the validity of the LNT. Always the answers are the same. Although some individual scientists have supported the existence of a threshold, there is currently no conclusive evidence that health risks don't exist at low levels of radiation exposure. In fact, the majority of radiobiologists can offer no biological mechanism to explain why there should be a threshold, irrespective of whether there are off-setting beneficial effects. The report indicates that this lack of conclusive scientific evidence has led the EPA and NRC to establish differing exposure limits. However, it is not the scientific evidence the has led to these differences. Both EPA and NRC use the LNT model. Rather, the different exposure limits are due to the risk management decisions that the agencies have made

Recycled/Recyclable • Printed with Vegetable Oil Based Inks on 100% Recycled Paper (40% Postconsumer)



ED_002751_00006820-00048

2

based on differing statutory mandates. Regardless, EPA is following with interest the current research in this area, in particular the research that the Department of Energy is currently funding to examine the sub-cellular processes that lead to radiogenic cancer. As noted in the report, EPA is also co-sponsoring a new National Academy of Sciences study to examine new evidence of radiation risk at low doses (the BEIR VII study).

See comment 2.

Your report also cites low-level radiation as a weak carcinogen and footnotes that low-level radiation accounts for far less than one percent of the cell-altering events that occur daily in cells. This assertion completely ignores the evidence that the type of damage done by ionizing radiation has a much higher probability of resulting in DNA misrepair than other normally occurring cell-altering events.

Ground Water Protection at Yucca Mountain

Next, I would like to comment on the difference in the radiation standards proposed for Yucca Mountain by EPA and NRC. Your report correctly reflects that EPA strongly supports separate ground water protection in its Yucca Mountain standards, as well as for other radiation protection standards for waste disposal sites, while NRC endorses the all pathways approach. The Agency, as well as the current and previous Administrations, has maintained the position to protect ground water for several reasons. The first and most obvious reasons are consistent and equitable public health protection. For example, the recently-licensed Waste Isolation Pilot Plant in New Mexico was afforded a ground water protection standard for disposal of transuranic radioactive waste. Virtually every state has taken steps toward comprehensive ground water protection. Forty-nine states have developed programs to protect current ground water sources of drinking water through the Wellhead Protection Program. Forty-one states have numeric or narrative ground water standards to help differentially protect their ground water supplies. EPA believes Yucca Mountain and the citizens of Nevada should be extended the same protection for the disposal of spent nuclear fuel and high level radioactive waste. Second, EPA believes that ground water in a region growing as rapidly as the Las Vegas metropolitan area should be protected from pollution "up front," rather than becoming polluted, and then forcing the residents to bare the cost of the environmental clean-up afterwards.

See comment 3.

Finally, EPA has not seen any documentation in DOE's own technical analyses that has shown that, even with separate ground water protection, Yucca Mountain cannot meet EPA's standards. We understand that these are preliminary analyses, and DOE still has to undergo the NRC licensing process; however, to date, DOE's most rigorous studies show compliance with the ground water standard by at least an order of magnitude. As our economic impact analysis for our final standards will illustrate, DOE's costs for the facility are driven by many external influences all striving to enhance repository safety. Some more notable influences include the Nuclear Waste Technical Review Board and the rigorous NRC licensing process. EPA's ground water standard alone is not responsible for driving the cost of Yucca Mountain; it is one of many



ED_002751_00006820-00049

3

safety factors DOE has considered as it has developed the repository. In fact, relative to the 20-year history of Yucca Mountain, EPA's standards have had little time to influence the overall cost of the program in any significant way.

MOU with NRC on Clean-up of NRC-Licensed Sites

See comment 4.

Our third area of disagreement with the report's conclusions is that the efforts towards developing a Memorandum of Understanding (MOU) with the NRC on the clean-up of NRC-licensed sites have had little progress. While this has not been an easy process, our two agencies have made substantial progress recently towards clarifying our respective roles in the cleanup and decommissioning of NRC- licensed facilities. It is premature to conclude that an MOU is unlikely.

See comment 5.

As a final comment, we note that the report, in Table 1, accentuates the large differences in costs between cleaning up a site to a 100 millirem per year standard or to a less than 10 millirem per year standard (including 1 millirem). We believe these comparisons are misleading. The relevant difference should be between the middle two columns, 25 millirem and 15 millirem, which represent the difference that NRC and EPA have often argued about. The cost difference between these two levels is actually very small and, if the Nevada Test Site example is ignored, one might be tempted to say negligible. We believe that NRC's application of the "as low as reasonably achievable" or ALARA approach will likely eliminate even these small cost differences. A more relevant cost difference would be the additional cost of meeting EPA's ground water standard. The rationale for this standard has been discussed above, but it is worth noting that by NRC's own estimation, ground water contamination would only be a concern at a very few nuclear power plant sites.

If you have any questions regarding these comments, please contact Frank Marcinowski at (202) 564-9290.

Sincerely,

Stephen D. Page, Director
Office of Radiation and Indoor Air



ED_002751_00006820-00050

The following are GAO's comments on the letter dated June 13, 2000, from the Director, Office of Radiation and Indoor Air, Environmental Protection Agency.

1. EPA said the draft report raised the issue of whether the U.S. government should continue to use the linear model, and EPA said it is following the consensus of scientific organizations in doing so. EPA also said the lack of scientific evidence has not led to the agency's regulatory disagreement with NRC. Rather, according to EPA, the two agencies have made different risk-management decisions, based on differing statutory mandates. One of our report's objectives was to describe the scientific basis for U.S. radiation standards, which we found to be inconclusive. The report raises no expectation that the linear model will or should be soon superseded, pending the existence of better evidence of low-level radiation effects. We agree that risk management decisions made by EPA and NRC, based on differing statutory mandates and protective strategies, largely account for the disagreement between the two agencies. Our report says this.

2. EPA said that in citing low-level radiation as a weak carcinogen, GAO ignored evidence that ionizing radiation has a much higher probability of resulting in DNA misrepair than other, more commonplace cell-altering events. We are aware of such evidence, and in agreement with EPA's qualifying point, we modified the final report accordingly.

3. EPA said that its groundwater standard is not alone responsible for driving the cost of the Yucca Mountain project, and EPA's standards have had little time to influence the overall cost of the program. Our report mentions several factors, significantly but not exclusively including EPA's proposed groundwater standard, that have influenced the project's costs to date and could do so in the future.

4. EPA said it is premature to conclude that a memorandum of understanding clarifying EPA's and NRC's regulatory roles is unlikely. We believe that, given the lack of progress by the two agencies since as long ago as 1992, it is questionable whether they will finalize such a memorandum. Even if they do, we question whether such a finalized memorandum will fundamentally resolve the problem between them.

5. EPA said the draft report should have focused more on the relatively small differences in cleanup costs between the 25-millirem-a-year and 15-millirem-a-year levels, which EPA and NRC have often argued about. The scope of our review did not exclude consideration of levels both higher and



ED_002751_00006820-00051

lower than 25 millirem a year and 15 millirem a year. The report shows that cost differences to achieve these levels vary, depending on the site involved, and may be small in some cases. However, in relation to the hundreds of potential cleanup sites that exist nationwide, overall cost differences between the 25-millirem-a-year and 15-millirem-a-year levels could be substantial.



ED_002751_00006820-00052

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

JUN 12 2000

OFFICE OF
SOLID WASTE AND EMERGENCY RESPONSE

Mr. Jim Wells, Director
Energy, Resources, and Science Issues
United States General Accounting Office
441 G Street NW
Room 2T23
Washington, D.C. 20548

Dear Mr. Wells:

I would like to express my appreciation for the opportunity to provide comments on the draft report "Low-Level Radiation Standards: Scientific Basis Inconclusive, and EPA and NRC Disagreement Continues." The comments contained in this letter will be limited to those issues directly impacting Superfund. Comments related to Yucca Mountain standards and scientific basis for radiation risk assessments will be addressed in a separate letter from EPA's Office of Radiation and Indoor Air.

See comment 1.

**Risk harmonized radiation and chemical site cleanups**. The draft report appears to evaluate the issues related to cleanup of radiological contamination at sites without acknowledging that at almost all sites with significant radiological contamination there also exists non-radiological (chemical) contamination. It is EPA's policy under CERCLA to address radioactively contaminated sites in a manner that is consistent with our guidance for addressing chemically contaminated sites, except to account for the technical differences between radio nuclides and chemicals. We would like to make it clear that radioactive contamination is not singled out in CERCLA as amended or EPA regulations as a privileged pollutant for which EPA should allow exceedances above the carcinogenic risk range ($10^{-4}$ to $10^{-6}$) that was determined generally to be protective for other carcinogenic contaminants. Further, ground waters should be returned to beneficial reuse which includes meeting MCLs established under the Safe Drinking Water Act for all contaminants including radio nuclides within the ground water plume, where MCLs are relevant and appropriate. EPA is committed to using the full range of alternatives available to achieve cleanup of ground waters and in selecting cleanup goals that reflect reasonably anticipated land uses to attain cleanups that are protective of human health and the environment. EPA's experience with remediating Superfund sites has shown that these objectives are achievable with limitations on land use, and the use of institutional and engineering controls. EPA's regulatory philosophy continues to be that the public deserves the same level of protection for radiation as they expect and get for chemical contaminants. This seems particularly appropriate for CERCLA sites since much, if not most, of the radiological contaminants are co-mingled with chemical contaminants.

Printed on Recycled Paper



ED_002751_00006820-00053

-2-

See comment 1.

**Consistent risk management approach within the Administration.** The draft paper should clarify further that in regards to the risk management approach for cleaning up sites, the agencies within the Administration (which includes EPA, DOE and DOD, but excludes NRC) are generally consistent, both under the current CERCLA statute and pertaining to proposals for reauthorizing the CERCLA statute. When cleaning up their sites, including those sites not on the NPL, DOE and DOD have generally conducted response actions using CERCLA authority. On May 22, 1995, EPA and DOE jointly issued a "Policy on Decommissioning Department of Energy Facilities Under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA)." The purposes of that Policy includes to "ensure that decommissioning activities are protective of worker and public health and the environment, [and are] consistent with CERCLA . . ." The Policy establishes that DOE generally will treat decommissioning activities as CERCLA removal actions, and that decommissioning response actions "should comply with the requirements of CERCLA, the NCP, and other applicable authorities." As explained in the policy, DOE's response actions will be consistent with CERCLA "regardless of whether or not the release or threatened release is from a site listed on the NPL." In addition, Section 120(a)(2) of CERCLA prohibits Federal Facilities (e.g., DOE, DOD) from adopting or utilizing any rule, guidance or criteria applicable to CERCLA remedial actions that are inconsistent with EPA CERCLA remedial action requirements. Also, the Administration's Superfund Legislative Reform Principles state that ". . . Maximum Contaminant Levels under the Safe Drinking Water Act or more stringent applicable State standards should be established as the cleanup standards for ground water whose beneficial use is or is anticipated to be as a drinking water source, unless technically impracticable."

See comment 2.

**Potential dual regulation at Sites.** The draft report seems to allege that there is confusion over possible dual regulation by EPA and NRC at several sites. Unfortunately, the report fails to discuss EPA's recent memorandum entitled "Interim Final Evaluation of Facilities Currently or Previously Licensed NRC Sites under CERCLA" (OSWER Directive 9272.0-15P) that was issued on February 17, 2000. This memo provides interim guidance to clarify EPA's role under CERCLA at facilities previously or currently licensed by NRC. If EPA finalizes an MOU with NRC in the future, EPA will revise this memorandum as necessary to reflect the coordination procedures agreed upon by NRC and EPA. In this interim guidance EPA states that "since September 8, 1983, EPA has generally deferred listing on the National Priorities List (NPL) sites that are subject to NRC's licensing authority because NRC's actions are generally believed to be consistent with the CERCLA requirement to protect human health and the environment."

See comment 2.

**EPA MOU negotiations.** We believe that the draft report inaccurately portrays EPA and NRC as making little progress in our MOU negotiations. The two agencies are in the process of working on a draft MOU and are continuing to make progress on finalizing a document. EPA's letter to the Appropriation Committee's direction to report on the status of MOU negotiations, which was established by the signing of the EPA's appropriation bill on October 20, indicated that the two Agencies were beginning to discuss possible language for an MOU. On May 23, 2000, NRC presented a draft MOU to EPA that incorporated much of earlier



ED_002751_00006820-00054

-3-

language that EPA had drafted and the two agencies discussed during a meeting on April 24. While meeting on May 23, EPA and NRC agreed to several changes to the NRC drafted MOU. On June 8, EPA transmitted to NRC several additional suggested changes for discussion with NRC during our next scheduled meeting of June 23. EPA believes that we are making progress in developing an MOU with NRC.

See comment 2.

**Potential congressional intervention on site cleanup issue**. The draft report several times raises the possibility of congressional intervention regarding EPA's and NRC's disagreement over acceptable cleanup levels for radioactively contaminated sites. The draft report fails to mention that the Administration has already opposed legislative provisions that would amend CERCLA to limit the role of the Superfund program at facilities currently or previously licensed by NRC. On September 3, 1997, former NRC Chairman Shirley Ann Jackson sent a letter to Senator John H. Chafee which proposed such legislative provisions to limit EPA's authority at NRC sites (see attached letter). In a March 25, 1998 letter to Senator Joseph Lieberman, EPA stated the Administration's opposition to NRC's draft legislative language, and reiterated EPA's position that development of an MOU by EPA and NRC, as opposed to legislative amendments to CERCLA, are the most appropriate process for addressing this issue (see attached letter). On July 21, 1999, EPA testified before the House Energy and Power Subcommittee opposing similar legislative provisions that were included in Section 207 of H.R. 2531 (see attached testimony). This testimony was followed with a letter on September 22, 1999 from EPA to Chairman Joe Barton answering several questions pertaining to EPA's opposition to NRC's legislative proposals (see attached letter).

See comment 3.

**Cost Analyses of site cleanup.** Although we have not had time to review the numerous studies cited in the draft report and are therefore unable to comment in detail, we find it difficult to believe that costs would begin to dramatically rise at the same cleanup level for different sites, particularly the level of soil to be addressed would be dependent upon such a variety of site-specific factors (e.g., land use selected, contaminants of concern at the site, how diffuse or discrete is the contamination, potential treatment technologies). In addition, it appears that most of these studies may not have been conducted to look at remedial alternatives in a manner consistent with CERCLA policy. Under CERCLA, a remedial alternative must meet the threshold requirements (protectiveness, compliance with ARARs). Cleanup levels that are not protective and ARAR compliant are screened out of the CERCLA process and not considered further, while the studies cited in the draft report contained primarily remedial alternatives that are not either protective or ARAR compliant. Therefore most of the studies cited in the draft report are not adequate for this type of analysis because they do not reflect the decision making process or choices that occur at CERCLA sites. In addition, **under CERCLA all remedies must be cost-effective**. Its overall effectiveness is then evaluated based on the following three balancing criteria: (1) long-term effectiveness and permanence, (2) reduction of toxicity, mobility, or volume through treatment, (3) short-term effectiveness. "Overall effectiveness is then compared to cost to ensure that the remedy is cost-effective. A remedy shall be cost-effective if its costs are proportional to its overall effectiveness" (see 55 FR 8850). Under current CERCLA policy, if a site cannot be cleaned up to a protective level (i.e., within the $10^{-4}$



ED_002751_00006820-00055

-4-

to $10^{-6}$ risk range) for the "reasonably anticipated future land use" because it is **not cost-effective or practicable** based, among other things, on an analysis of adverse effects on the environment or workers), then a **more restricted land use should be chosen that will meet a protective level**. (This may include use as a waste management area (OSWER Directive No. 9355.7-04 "Land Use in the CERCLA Remedy Selection Process," May 25, 1995, pp. 8-9).) This policy reflects the Administrator's CERCLA reauthorization position on land use. A number of the studies cited by the draft Report appear not to take this land use policy into account, and some of the studies actually predate the 1995 guidance on land use. Also, when not based on ARARs, remedies under CERCLA should be based on risk, rather than millirem. Most of the remedial alternatives cited in the draft report are expressed in millirem levels.

**Risk Assessment at CERCLA sites.** The draft report raises questions regarding the certainty of risk posed by radiation. The report discusses the possibility that both EPA and NRC are cleaning up sites under their regulatory authority to limit exposure to radiation to levels that science may eventually conclude is below a threshold level that poses a potential risk of cancer. Although this issue will be more fully explored in a letter from ORIA, we would like to point out that in the absence of ARARs that are sufficiently protective, cleanup levels at CERCLA sites are generally expressed in terms of risk levels, rather than millirem, as a unit of measure. CERCLA guidance recommends the use of slope factors in the EPA Health Effects Assessment Summary (HEAST) tables when estimating cancer risk from radioactive contaminants. Were the slope factors in HEAST to change, the actual site-specific concentrations that correspond to the risk range would change to reflect this change in science. Although EPA acknowledges uncertainty on the risks of radioactivity, there is more certainty for radiation risk then for almost any other pollutant. If in the future the current estimates of radiation risk were to change, the Superfund risk range would allow flexibility in reflecting those changes in actual cleanup decisions. In contrast, NRC would have to do a new rulemaking to reflect updated risk estimates.

If you have any questions regarding our comments, please contact Stuart Walker of my staff at (703) 603-8748.

Sincerely,

Stephen D. Luftig, Director
Office of Emergency and Remedial Response

Enclosure:

cc:
Steve Page



ED_002751_00006820-00056

The following are GAO's comments on the letter dated June 12, 2000, from the Director, Office of Emergency and Remedial Response, Environmental Protection Agency.

1. EPA said the draft report appears to evaluate radiological site contamination and cleanup issues without sufficient acknowledgement that chemical contamination also exists at almost all of these sites. Although the subject of our report is radiation protection, the report states that EPA's policy is to coregulate chemicals and radionuclides, within the same risk range, rather than to treat them differently. EPA also said its risk management approach for cleaning up sites is generally consistent with that of other agencies, including DOE (but not NRC). Although our report focused mainly on regulatory differences between the two principal standard-setting agencies, EPA and NRC, the report points out that NRC and DOE (in its worker protection standards and proposed public protection standards) generally favor a "top down" approach of setting a relatively less restrictive dose limit, and then reducing doses well below the limit in site-specific situations. On the other hand, EPA's Superfund approach has been "bottom up," setting a relatively restrictive risk goal but allowing less restrictive limits in site-specific situations.

2. EPA said the draft report does not adequately discuss recent EPA-NRC initiatives to avoid potential dual regulation at cleanup sites and inaccurately portrays the two agencies as making little progress in negotiating a memorandum of understanding. Our draft report refers to these recent initiatives, but we modified the final report to make more specific mention of them. Overall, in relation to the EPA-NRC disagreement and these initiatives, our report essentially takes the longer view, noting that since as long ago as 1992, the two agencies have been unsuccessful in addressing their potentially conflicting roles in site cleanups. On this basis, it is unclear that the latest initiatives will succeed without congressional intervention. EPA also said the draft report fails to mention the administration's opposition to proposed legislative changes, such as amending Superfund legislation, in lieu of the memorandum of understanding approach. While we are aware of past legislative proposals, our report does not delineate what form congressional clarification of the two agencies' regulatory responsibilities might take.

3. EPA doubted that nuclear site cleanup costs would begin to dramatically rise at the same cleanup level for different sites. Our report makes no such assertion. In general, the agency analyses we examined showed faster rising costs at lower cleanup levels.



ED_002751_00006820-00057

# Comments From the Nuclear Regulatory Commission

UNITED STATES
NUCLEAR REGULATORY COMMISSION
WASHINGTON, D.C. 20555-0001

CHAIRMAN

June 9, 2000

Mr. James Wells, Director
Energy, Resources and Science Issues
Resources, Community,
and Economic Development Division
United States General Accounting Office
Washington, D. C. 20548

Dear Mr. Wells:

I am responding to your June 2, 2000, letter and the enclosed draft report to Senator Domenici (GAO/RCED-00-152), addressing the scientific basis and costs of U. S. radiation standards at low levels, and differences between the standards of the U.S. Environmental Protection Agency (EPA) and the U.S. Nuclear Regulatory Commission (NRC). We believe that this is a fundamentally sound report, which should help Congress understand the long-standing differences between the agencies, differences which we have thus far been unable to bridge. We support your conclusions that the Federal agencies should agree on decommissioning and high-level waste policies and approaches to ensure consistent standards and public protection.

As you note in the report, the regulatory standards that the NRC promulgated for decommissioning arrived at dose criteria with ample safety margins, protective of all pathways, including groundwater, with a cost-benefit analysis that allows for site-specific evaluation. EPA takes a different approach. The NRC is continuing to discuss the differences in decommissioning policies with the EPA in an attempt to eliminate the potential for dual regulation at sites undergoing decommissioning. We agree that Congressional resolution of lead Federal agency regulatory authority may be necessary if the NRC and the EPA are unsuccessful at resolving their differences.

Your report also notes that the NRC-proposed high-level waste standards for Yucca Mountain apply the all-pathways approach, which has been supported by the National Academies of Sciences and other commenters. EPA's addition of a separate groundwater standard lacks technical support and applies drinking water concentration limits to groundwater at the repository that are outdated and that present non-uniform risks. Here, too, reconciliation of the differences in approach may require Congressional action.

As page 3 of your report correctly points out, ground water protection is a central issue between NRC and EPA both at Yucca Mountain and the cleanup and decommissioning of licensed sites. EPA chooses to apply certain standards to groundwater that were developed to apply "at the tap" to public drinking water supplies pursuant to the Safe Drinking Water Act (SDWA). This application of SDWA's standards to groundwater is questionable. Moreover, NRC believes that EPA may be fundamentally misinterpreting Congressional intent with regard to the "anti-backsliding" provision of the SDWA (42 U.S.C. 300g-1(b)(9)). NRC believes that Congress never intended this provision to preclude the use of up-to-date scientific information to translate the 4 millirem/yr regulatory limit in EPA's drinking-water regulations (40 CFR



ED_002751_00006820-00058

-2-

141.16), into radionuclide-specific concentration limits. Instead, as your report also correctly points out, EPA uses an outdated 1959 dose methodology (by reference to National Bureau of Standards Handbook 69), which results in doses for individual radionuclides that vary by orders of magnitude, with many of crucial importance well below 4 millirem/yr (e.g., 0.07 millirem/yr for Strontium-90 and 0.2 millirem/yr for Iodine-129). The NRC believes that a reasonable interpretation of the statute might require EPA to maintain the 4 millirem/yr standard, but would allow EPA discretion to determine the appropriate approach for calculating compliance consistent with current scientific understanding. The normalization of all radionuclide concentration limits to 4 millirem/yr total effective dose equivalent, using current scientific methodologies, would go part way to resolving the differences between the two agencies. As a result, we strongly suggest a recommendation be added to your report that Congress may wish to clarify its intent in enacting the SDWA's "anti-backsliding" provision.

The final resolution to these issues should also ensure that Federal standards for radiation protection provide protection of public health consistent with state-of-the-art scientific methodologies. There is general consensus that health effects from radiation exposures at the current 100 mrem/yr public dose limit, or below, are indistinguishable from health effects from other everyday risks encountered by the general public. In addition, the current NRC occupational exposure limit, at a level 50 times higher than the national non-occupational dose limit, is deemed to be protective of workers' health. Studies have not demonstrated deleterious health effects from occupational radiation exposures at the current limit.

Specific recommended changes to the text of the report are enclosed for your consideration. These changes should clarify the findings in your report.

Again, we believe the report is fundamentally sound and should prove helpful. I look forward to receiving the final version.

Sincerely,

Richard A. Meserve

Enclosure:
Mark-up of Recommended Changes
to GAO Draft Report



ED_002751_00006820-00059

# Comments From the Department of Energy

Note: GAO comments supplementing those in the report text appear at the end of this letter.

**Department of Energy**
Washington, DC 20585
June 13, 2000

Mr. Jim Wells, Director
Energy, Resources and Science Issues
United States General Accounting Office
Washington, DC 20548

Dear Mr. Wells:

This is in response to your letter of June 2, 2000, to Secretary Richardson regarding the review of your draft report on low level radiation standards for Senator Domenici. In general, we found the report factual and balanced. We have no major disagreements with the report and the attached comments are intended to clarify discussions in the report or to emphasize issues that were not fully discussed.

Thank you for the opportunity to review the report. If you have any questions regarding these comments please contact Andrew Wallo at 202-586-4996.

Sincerely,

David Michaels, PhD, MPH
Assistant Secretary for
Environment, Safety and Health



ED_002751_00006820-00060

**DOE Comments on Draft GAO Report**
**"Low -Level Radiation Standards"**

In general, the Department found the subject report factual and balanced in its presentation. We look forward to completion of the final report. We provide the following general and specific comments for the purposes of clarification.

The Department of Energy, unlike most other organizations, operates facilities that are subject to radiation protection standards issued by several agencies including its own. The Department is responsible for cleanups and waste management operations that must comply with DOE requirements, with CERCLA and RCRA requirements and, in some cases, requirements issued by NRC. Most DOE requirements are similar to those of the NRC. Cleanups under DOE requirements and guidance must meet the 25 mrem/year plus ALARA requirements similar to NRC's 10 CFR Part 20 requirements. At the same time, we have sites (actually most of our cleanups) that are remediated under CERCLA requirements where the $10^{-6}$ to $10^{-4}$ risk range must be met. At many of these facilities the 15 mrem/y limit has been used as the cap for the risk range. For the most part both systems (the NRC/DOE approach and the EPA approach) work and produce protective actions with reasonably similar results. The disagreement over these two approaches is continuously discussed in terms of 25 mrem vs 15 mrem or 100 mrem/y all sources vs $10^{-6}$ to $10^{-4}$ lifetime risk range for specific activities. For the most part this does not truly define the problem or the real issue. The real issue is whether the standard, in addition to being protective, is flexible enough to ensure it does not bring about in actions that cause more harm than good or that have costs that are not commensurate with the benefit they may provide.

As the GAO report noted, it is in the area of groundwater protection where large differences arise. The report characterizes the issue reasonably well by indicating EPA's preference to use tap water standards as groundwater protection standards on the basis of policy without supporting cost/benefit analyses or without assessing alternatives for their application to ground water. NRC and DOE have not been able to justify the use of this policy and instead protect ground water as one element of the "all pathways" assessment. The draft GAO report notes (1) that the specific numerical limits are obsolete because of newer dosimetric models (pages 16-17) and that (2) the "no backsliding" provisions of the 1996 Safe Drinking Water Act Amendments may rule out raising the limits for radionuclides (page 18 also see specific comment). What is not mentioned in the draft report is that these differences are at least in part due to enabling legislation. Under their AEA authority NRC and DOE are charged to protect the public and environment and can do it through an all pathways approach. However, under some EPA implemented legislation Congress has specifically endorsed the use of the tap water standard approach for ground water (i.e., RCRA and CERCLA) by specify that the drinking water standards should be used for non-degradation of groundwater. EPA has expanded this approach into areas outside of RCRA and CERCLA.

Throughout the report, there are statements that report the conclusions of interviews with various individuals and organizations and others that report specific facts or technical conclusions (including dose and cost estimates). We understand that this is a draft report and assume the references will be in the final report. We recognize most of the information but feel clear references will improve the report's credibility and assist readers not as familiar with the topic.

See comment 1.



ED_002751_00006820-00061

**Specific Comments:**

Report Title: As written the title could be misunderstood to imply the report applies to low-level radioactive waste. GAO may wish to consider a title along the lines "Standards Regulating Exposures to Low Levels of Radiation."

Page 6, line 16: Suggest changing "nuclear waste storage" to "nuclear waste disposal."

Page 8, footnote 12: The footnote on page 8 incompletely cites the degree of confidence of the cancer estimates of the 1990 BEIR study. The footnote states that, for 100 millirem per year over a lifetime at the 90 percent confidence interval, the number of additional deaths per 100,000 people is 410 to 980 for men and 500 to 930 for women. Pages 180 and 181 of the BEIR V report make clear that these confidence intervals assume the validity of the linear model and only reflect the uncertainty of the inputs to that model. As the BEIR report states on page 181: "Moreover, epidemiological data cannot rigorously exclude the existence of a threshold in the millisievert dose range. Thus the possibility that there may be no risks from exposures comparable to external natural background radiation cannot be ruled out. At such low doses, it must be acknowledged that the lower limit of the range of uncertainty in the risk estimates extends to zero."

Page 9: Figure 1 is presented as an illustration of the linear no threshold concept and to clarify the remark below the table "that as exposure doubles, risk doubles..." Inclusion of units or divisions on the table or redrawing the line at a 45 degree angle showing a 1:1 slope would help the illustration for readers not familiar with the topic.

Page 11, " Research Efforts to Verify Low-Level Radiation Effects are On-going", paragraph 3: This paragraph explains the conduct of epidemiologic studies and refers to case-control and ecologic studies but omits any reference to cohort studies (such as the study of atomic bomb survivors). The following changes in the second and third sentences that will also make the wording consistent with that in Appendix IV are recommended:

"In this regard, epidemiologists consider two types of epidemiologic studies **1) analytic or 2) ecologic. Analytic studies either compare individuals who have received an exposure to an agent such as radiation to those individuals who were not exposed and determine if there are subsequent differences in their health status (cohort studies) or** compare individual cases of disease to a **comparison set of individuals who do not have the disease to determine if there were differences in the past exposures of these two groups** (case control studies). Ecologic studies rely on regional data on disease and radiation levels instead of individual data**, and are considered** to be less reliable **than analytic studies**."

Also the last sentence of the second paragraph of Appendix IV needs editing. The word "funded" should be deleted where it appears for the second time in that sentence.

Page 14, lines 13 and 14: Suggest changing "national decision will be made in coming months" to



ED_002751_00006820-00062

"national decision will be made in 2001."

Page 18, paragraph 1: This paragraph correctly notes EPA's interpretation of the "no backsliding" provision of the 1996 Safe Drinking Water Act Amendments; however, it may also be important to note that based on a review of the Congressional record and the legislation, others have a somewhat different interpretation of these provisions. One interpretation is that Congress was directing EPA to use the best possible science in developing and updating standards and that the provision should be applied to the dose or risk goals not the concentration limits that are a product of the dose/risk goal and the science. The way the provision is interpreted could have significant impact in many areas.

See comment 2.

Pages 18-21 (and Appendix V): The discussions here and the appendix discuss the relationship between costs and dose but do not address the integrated health risk or detriment associated with or averted by the standards and associated cleanup levels. Using the LTN model, at most sites the integrated cancer risk (individual risk x number of individuals at risk) is typically less then one at all dose limit levels; suggesting zero expected cancers for most site-specific cleanup alternatives. Therefore, reducing "risk" below the 25/15 mrem levels provides little if any health benefit. Even when the hypothetical risks averted are added for all sites to produce numbers in excess of one, there are generally small differences between 25 mrem vs.15 mrem dose limits. As noted in our general comment the important issue is the flexibility of the regulatory system.

See comment 3.

Page 23, line 9: Change "would" to "may." The sentence would read "...such a design may not be needed..." This would indicate that the decision is not absolute, at this time.

Page 23, line10: Suggest changing "less restrictive standards such as" to a "more flexible all-pathway standard." This would clarify the NRC and DOE preference not to have a separate groundwater standard.

Page 31: The draft report states that the cleanup criterion for radium-226 is 5 picoCuries per gram. In reality, the criteria for both radium-226 and radium-228 is 5 picoCuries per gram in the surface soil and 15 picoCuries per gram in the subsurface soil. Also, we presume that because DOE requirements (excepting 10 CFR Part 835) are published in DOE Orders and this table only lists requirements published in the Code of Federal Regulations, DOE requirements are not included. For the record, we do note that DOE radiation control requirements for public protection are in DOE 5400.5 and for waste management in DOE O 435.1.

Page 34, 2nd paragraph, 2nd to last sentence: Change sentence "Results are expected in mid to late summer 2000." to: "Results are expected in late 2000."

Appendix IV: GAO may also want to summarize the Navy shipyards study in the report because it is one of the largest low dose epidemiological studies completed in the United States. In 1991, researchers from the Johns Hopkins University, Baltimore, Maryland, completed a comprehensive epidemiological study of the health of workers at the six Navy shipyards and two private shipyards that serviced Navy nuclear-powered ships. This independent study evaluated a population of 70,730 civilian workers over a period from 1957, beginning with the first overhaul



ED_002751_00006820-00063

of the first nuclear-powered submarine (USS NAUTILUS) through 1981, to determine whether there was an excess risk of leukemia or other cancers associated with exposure to low levels of gamma radiation.

This study did not show any cancer risks linked to radiation exposure. Furthermore, the overall death rate among radiation-exposed shipyard workers was less than the death rate for the general U.S. population. It is well recognized that many worker populations have lower mortality rates than the general population, because the workers must be healthy to perform their work. This study shows that the radiation-exposed shipyard population falls in this category. In conclusion, the Johns Hopkins study found no evidence to conclude that the health of people involved in work on U.S. nuclear-powered ships has been adversely affected by exposure to low levels of radiation incidental to this work.

Appendix V (and the discussion on pages 21-26): As this data shows the difference in costs in the 25 to 15 mrem/y cleanup limit ranges is marginal and is many times within the uncertainty of these estimates. It is usually only as one moves to significantly higher or lower doses that differences in cost become very significant. Although there are a few situations (sites) where the differences between 25 mrem and 15 mrem are significant, the fact is that given the nature of cleanup activities, a cleanup to 25 mrem or 15 mrem all-pathways limit normally achieves protection from actual use well below either level. (Also see previous comment on risk relating to the discussion on pages 18 through 21).



ED_002751_00006820-00064

The following are GAO's comments on the Department of Energy's letter dated June 13, 2000.

1. DOE raised the question of references to information sources in our draft report. Our report, for the most part, does not cite technical sources, in keeping with GAO's policy and the role of our reports as other than technical treatises, as well as in the interest of report brevity.

2.DOE said there may be different interpretations of the "no backsliding" provision of the 1996 Safe Drinking Water Act Amendments. We believe that groundwater protection policy and legal matters, including the specific "no backsliding" provision, will be of interest to the congressional committees of jurisdiction in any efforts they may wish to undertake to reconcile EPA's and NRC's regulatory approaches.

3. DOE said the draft report did not address the integrated health risk or detriment associated with or averted by the standards and associated cleanup levels, and it pointed out that risk reductions associated with cleanup efforts may provide little if any health benefit. Our report recognizes that agencies routinely calculate hypothetical cancer deaths averted in achieving cleanup levels. However, we regard such calculations with caution because they are based on the linear model, and therefore we did not highlight such calculations in our report.



ED_002751_00006820-00065

## Ordering Information

The first copy of each GAO report is free. Additional copies of reports are $2 each. A check or money order should be made out to the Superintendent of Documents. VISA and MasterCard credit cards are accepted, also.

Orders for 100 or more copies to be mailed to a single address are discounted 25 percent.

*Orders by mail:*
U.S. General Accounting Office
P.O. Box 37050
Washington, DC 20013

*Orders by visiting:*
Room 1100
700 4th St. NW (corner of 4th and G Sts. NW)
U.S. General Accounting Office
Washington, DC

*Orders by phone:*
(202) 512-6000
fax: (202) 512-6061
TDD (202) 512-2537

Each day, GAO issues a list of newly available reports and testimony. To receive facsimile copies of the daily list or any list from the past 30 days, please call (202) 512-6000 using a touchtone phone. A recorded menu will provide information on how to obtain these lists.

*Orders by Internet:*
For information on how to access GAO reports on the Internet, send an e-mail message with "info" in the body to:

info@www.gao.gov

or visit GAO's World Wide Web home page at:

http://www.gao.gov

## To Report Fraud, Waste, or Abuse in Federal Programs

*Contact one:*

- Web site: http://www.gao.gov/fraudnet/fraudnet.htm
- e-mail: fraudnet@gao.gov
- 1-800-424-5454 (automated answering system)

PRINTED ON RECYCLED PAPER

ED_002751_00006820-00066

United States
General Accounting Office
Washington, D.C. 20548-0001

Official Business
Penalty for Private Use $300

Address Correction Requested

Bulk Rate
Postage & Fees Paid
GAO
Permit No. GI00

Message

**From**: Woods, Clint [woods.clint@epa.gov]
**Sent**: 11/28/2018 3:59:41 PM
**To**: Konkus, John [konkus.john@epa.gov]
**Subject**: FW: Ed Calabrese

FYI – Draft response below

# Ex. 5 Deliberative Process (DP)

Clint Woods
Deputy Assistant Administrator
Office of Air and Radiation, U.S. EPA
202.564.6562

**From:** Rust, Susanne [mailto:susanne.rust@latimes.com]
**Sent:** Wednesday, November 21, 2018 12:05 PM
**To:** Woods, Clint <woods.clint@epa.gov>
**Subject:** Re: Ed Calabrese

Thanks for your reply.
Any thoughts about when that might happen? And anyone in particular I should reach out to?
Appreciate your help.
Susanne Rust

On Nov 21, 2018, at 7:35 AM, Woods, Clint <woods.clint@epa.gov> wrote:

> Ms. Rust,
>
> Thanks so much for your email - Our press team will be in touch.
>
> Clint
>
> On Nov 20, 2018, at 12:33 PM, Rust, Susanne <susanne.rust@latimes.com> wrote:
>
> > Dear Mr Woods,
> >
> > I'm a reporter at the Los Angeles Times working on a story about hormesis, Ed Calabrese, LNT and the EPA's proposed new rule on transparency in science.
> > I came across some emails you exchanged with Dr. Calabrese this spring about LNT. According to the chronology, you sought Calabrese's advice on what to incorporate into the rule, you spoke, and he also provided you with language to use, which was then incorporated into the rule - word-for-word.
> > I wonder if you could answer some questions about this exchange for me?

1) Who suggested you contact Calabrese?
2) What other toxicologists/scientists did you consult with?
3) In one of your emails, you mentioned that you and Calabrese had known one another years ago. Can you tell me how?

Thanks for your time. Feel free to call me at: 650-804-6790.

Susanne Rust

Reporter, The Los Angeles Times
650-804-6790

Message

**From:** Danylak, Mike (EPW) [Mike_Danylak@epw.senate.gov]
**Sent:** 10/1/2018 7:52:25 PM
**To:** Danylak, Mike (EPW) [Mike_Danylak@epw.senate.gov]
**Subject:** EPW to Hold Subcommittee Oversight Hearing on the EPA's Use of Sound and Transparent Science
**Attachments:** ATT00001.txt

For Immediate Release:
October 1, 2018

Contact: Mike Danylak ~202.224.1049
Mike_Danylak@EPW.Senate.Gov

# ***MEDIA ADVISORY***

## EPW to Hold Subcommittee Oversight Hearing on the EPA's Use of Sound and Transparent Science

WASHINGTON, D.C. — On Wednesday, October 3 at 2:15 PM EDT, the Senate Committee on Environment and Public Works (EPW) subcommittee on Superfund, Waste Management, and Regulatory Oversight will hold a hearing titled, "Oversight of the Environmental Protection Agency's (EPA) Implementation of Sound and Transparent Science in Regulation."

**DETAILS:**

**WHAT**: A subcommittee oversight hearing titled, "Oversight of the Environmental Protection Agency's Implementation of Sound and Transparent Science in Regulation."

**WHEN**: 2:15 PM EDT, Wednesday October 3, 2018

**WHERE**: 406 Dirksen Senate Office Building

Live streaming video of the hearing will also be provided at http://epw.senate.gov

**WITNESSES:**

**Dr. Edward J. Calabrese**
Professor, University of Massachusetts at Amherst School of Public Health and Health Sciences

**Robert Hahn**
Visiting Professor, Oxford University Smith School of Enterprise and the Environment

**Dr. Rush D. Holt**

Chief Executive Officer, American Association for the Advancement of Science

###

**http://epw.senate.gov**
Twitter | YouTube

Message

**From**: Lynn, Tricia [lynn.tricia@epa.gov]
**Sent**: 9/13/2018 2:30:37 PM
**To**: Press [Press@epa.gov]; Konkus, John [konkus.john@epa.gov]
**CC**: Edwards, Jonathan [Edwards.Jonathan@epa.gov]; Veal, Lee [Veal.Lee@epa.gov]; Griggs, John [Griggs.John@epa.gov]
**Subject**: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

I'll run it through the OAR comms folks for response.

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Cc:** Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly

prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.

Message

**From**: Orquina, Jessica [Orquina.Jessica@epa.gov]
**Sent**: 4/24/2018 6:46:34 PM
**To**: Konkus, John [konkus.john@epa.gov]
**Subject**: RE: EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

Thanks!

Jessica Ann Orquina, Director
Office of Web Communications
U.S. Environmental Protection Agency
Email: orquina.jessica@epa.gov
Office: 202-564-0446
Mobile: Ex. 6 Personal Privacy (PP)

---

**From:** Konkus, John
**Sent:** Tuesday, April 24, 2018 2:46 PM
**To:** Orquina, Jessica <Orquina.Jessica@epa.gov>
**Subject:** RE: EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

Here's the link: https://www.epa.gov/newsreleases/epa-administrator-pruitt-proposes-rule-strengthen-science-used-epa-regulations

---

**From:** Orquina, Jessica
**Sent:** Tuesday, April 24, 2018 2:42 PM
**To:** Konkus, John <konkus.john@epa.gov>
**Subject:** RE: EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

Okay, thanks!

Jessica Ann Orquina, Director
Office of Web Communications
U.S. Environmental Protection Agency
Email: orquina.jessica@epa.gov
Office: 202-564-0446
Mobile: Ex. 6 Personal Privacy (PP)

---

**From:** Konkus, John
**Sent:** Tuesday, April 24, 2018 2:42 PM
**To:** Orquina, Jessica <Orquina.Jessica@epa.gov>
**Subject:** FW: EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

Jess: Here's the release if we can get it into the newsroom you can link it to your draft posts…

---

**From:** EPA Press Office [mailto:press=epa.gov@cmail19.com] **On Behalf Of** EPA Press Office
**Sent:** Tuesday, April 24, 2018 2:30 PM
**To:** Konkus, John <konkus.john@epa.gov>
**Subject:** EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

U.S. ENVIRONMENTAL PROTECTION AGENCY
NEWS RELEASE
WWW.EPA.GOV/NEWSROOM

# EPA Administrator Pruitt Proposes Rule To Strengthen Science Used In EPA Regulations

**WASHINGTON** (April 24, 2018) - Today, U.S. Environmental Protection Agency (EPA) Administrator Scott Pruitt signed a proposed rule to strengthen the science used in regulations issued by EPA. The rule will ensure that the regulatory science underlying Agency actions is fully transparent, and that underlying scientific information is publicly available in a manner sufficient for independent validation.

"The era of secret science at EPA is coming to an end," **said EPA Administrator Scott Pruitt**. "The ability to test, authenticate, and reproduce scientific findings is vital for the integrity of rulemaking process. Americans deserve to assess the legitimacy of the science underpinning EPA decisions that may impact their lives."

This proposed rule is in line with the scientific community's moves toward increased data sharing to address the "replication crisis"—a growing recognition that a significant proportion of published research may not be reproducible. The proposal is consistent with data access requirements for major scientific journals like *Science*, *Nature*, and *Proceedings of the National Academy of Sciences* as well as recommendations from the Bipartisan Policy Center's Science for Policy Project and the Administrative Conference of the United States' Science in the Administrative Process Project.

The proposed rule builds upon President Trump's executive orders on regulatory reform and energy independence:

- **Executive Order 13777**, issued in March 2017, provides that regulatory reform efforts shall attempt to identify "those regulations that rely in whole or in part on data, information, or methods that are not publicly available or that are insufficiently transparent to meet the standard of reproducibility."
- **Executive Order 13783**, also issued in March 2017, provides that "It is the policy of the United States that necessary and appropriate environmental regulations comply with the law, are of greater benefit than cost, when permissible, achieve environmental improvements for the American people, and are developed through transparent processes that employ the best available peer-reviewed science and economics."

**Chairman Lamar Smith (R-TX):** "Administrator Pruitt's announcement ensures that data will be secret no more. For too long, the EPA has issued rules and regulations based on

data that has been withheld from the American people. It's likely that in the past, the data did not justify all regulations. Today, Administrator Pruitt rightfully is changing business as usual and putting a stop to hidden agendas."

**Senator Mike Rounds (R-SD)**: "Sound, reliable science is vital to helping us make important policy decisions that impact the health of American families and their livelihoods. Inserting new levels of transparency in the EPA rulemaking process will help make the agency more accountable to the American people and help everyone understand the impact of EPA's decisions. Today's directive is a significant step toward making sure these decisions are not made behind closed doors with information accessible only to those writing the regulations, but rather in the full view of those who will be affected."

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts**: "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process."

**Dr. Louis Anthony (Tony) Cox, President, Cox Associates; Member, National Academy of Engineering; and Editor-in-Chief of the Journal *Risk Analysis***: "I believe that transparency and independent reproducibility of analyses and conclusions are bedrock principles of sound science. Some commentators have expressed concerns that making the data behind policy conclusions and recommendations accessible and transparent might threaten the privacy of individuals. But this concern can be fully met by applying current privacy-protection techniques for data analysis. These techniques have been developed and used successfully for years at the Census Bureau and elsewhere. Thus, we can have the scientific benefits of accessible data while protecting individual privacy."

**Dr. Jason Scott Johnston, Director, Olin Law and Economics Program, University of Virginia School of Law**: "EPA's proposed rule, Strengthening Transparency in Regulatory Science, is badly needed "Best practice among peer-edited scientific journals is to require that data and statistical routines used in published papers be posted online and/or made publicly available. To apply the same standards to research that EPA says justify regulations affecting billions of dollars in economic activity and millions of human lives is essential for those regulations to truly be scientifically based."

**Bruno Pigott, Commissioner of the Indiana Department of Environmental Management (IDEM)**: "IDEM supports transparency in rulemaking. Good, sound science leads to better regulations."

**Dr. George Wolff, Principal Scientist, Air Improvement Resource, Inc., and former Chairman of EPA's Clean Air Scientific Advisory Committee (1992 – 1996)**: "In the development of regulations based on environmental studies, numerous subjective assumptions and choices must be made regarding the selection of data and models that

have a profound impact on the strength of any statistical associations and even whether the associations are positive or negative. The appropriateness of the assumptions and choices are not adequately evaluated in the standard peer review process. That is why it is essential that the data and models be placed in the public domain for a more rigorous evaluation by qualified experts. The proposed regulation, Strengthening Transparency in Regulatory Science, will provide an opportunity for such evaluations."

###

Visit The EPA's Newsroom

U.S. Environmental Protection Agency
1200 Pennsylvania Avenue Northwest
Washington, D.C. 20004

Like
Tweet
Share
Forward

Unsubscribe

Message

**From**: Rust, Susanne [susanne.rust@latimes.com]
**Sent**: 11/8/2018 8:45:13 PM
**To**: Block, Molly [block.molly@epa.gov]
**CC**: Press [Press@epa.gov]
**Subject**: Re: Strengthening Transparency in Regulatory Science/ Media request

Thanks - although I think we can both agree this is not answering the questions I asked.
Again, I asked: 1) what was the role that Steve Milloy and Edward Calabrese played in crafting the rule; and 2) who solicited their input?

I am not asking about public comments. I am not asking about what the EPA thinks of these comments. I am asking about the rule, how it was written, whose advice was solicited, and why? Again, see above.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 12:38:46 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

As we've previously stated: You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on these issues, and EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:16 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 11:15:28 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

I should have something for you shortly.

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:13 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

Would it be fair to say the EPA declined to comment on Milloy and Calabrese's influence on the proposed ruling? Or will you have a response.
Thank you.
Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 7:24:49 AM
**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

I have information suggesting that Steve Milloy and Edward Calabrese were instrumental in crafting the ruling's suggestion to incorporate risk models other than LNT.
I wonder if you could tell me what their role was in crafting the rule and and who solicited their input?
Thank you.
Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 6:27:41 AM
**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Understood. Still wondering when a final ruling or decision is expected?

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 6:27:01 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

As we've stated before, we are currently reviewing 590,000 public comments on the proposal.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 9:26 AM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi -

Any idea when the EPA will make a decision or submit a final ruling?

Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 1:14:50 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

This should be helpful for you:

The proposed regulation takes comment on ensuring transparency and consideration of high quality studies evaluating models and model assumptions, including high quality studies that examine different potential dose-response relationships. You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on particular studies, and the EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Wednesday, November 7, 2018 3:18 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi

Ha. No. I'm not suggesting any new models. Just wondering what this is based on and why it's being incorporated? There's a discussion in the ruling about doubts re linearity non threshold models, and I'm curious about it's origin and why it's included in a ruling that seems to be mostly about transparency and open data? And what this would mean for the way EPA evaluates an performs risk assessments?
Thanks. Susanne

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 11:58 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

Do you have specific questions? Or are you interested in any specific models? The transparency rule does not ask for the public to suggest or otherwise comment on "new models to evaluate risk assessment."

I'm happy to help, just trying to figure out the best way to answer your inquiry.

Molly

Begin forwarded message:

**From:** "Rust, Susanne" <susanne.rust@latimes.com>
**Date:** November 7, 2018 at 8:37:03 AM EST
**To:** "daguillard.robert@epa.gov" <daguillard.robert@epa.gov>
**Subject: Strengthening Transparency in Regulatory Science/ Media request**

Dear Mr. Daguillard,

I am working on a story about the "Strengthening Transparency in Regulatory Science" proposal and I am hoping I can get some information and maybe a comment?
I am particularly interested in the proposed rule's request for new models to evaluate risk assessment.
Any chance you can talk today? Or can you put me in touch with someone who can tell me how this came about and why? My deadline is tomorrow at noon.
Thank you.
Susanne Rust

Reporter, Los Angeles Times
Ex. 6 Personal Privacy (PP)

Message

**From**: McClintic, Howard [McClintH@ctc.com]
**Sent**: 2/14/2018 3:45:06 PM
**To**: Kelly, Albert [kelly.albert@epa.gov]
**Subject**: RE: Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!

**Importance**: High

Thank you – I look forward to our Conference Call!

Administrator Pruitt is aware of this Project through Dr. Ed Calabrese, Co-Chair of the Project, as well as various professional and personal friends of his around-the-country.

Thank you again,

***Howard***

Ex. 6 Personal Privacy (PP)

---

**From:** Kelly, Albert [mailto:kelly.albert@epa.gov]
**Sent:** Wednesday, February 14, 2018 10:34 AM
**To:** McClintic, Howard
**Subject:** RE: Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!

Thank you. We will review and be in touch

Albert Kelly
Senior Advisor to the Administrator
1200 Pennsylvania Avenue, NW
Washington, DC 20460
202 306 8830

---

**From:** McClintic, Howard [mailto:McClintH@ctc.com]
**Sent:** Wednesday, February 14, 2018 10:30 AM
**To:** Kelly, Albert <kelly.albert@epa.gov>
**Subject:** Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!

CTC Foundation

***Ensuring the Future Through Innovation, Science and Technology***

1235 S. Clark St. Ste. 715
Arlington, VA 22202
(703) 310-5688 (703) 310-5655 FAX
Ex. 6 Personal Privacy (PP)
E-Mail: McClintH@ctc.com
Tax-Exempt Number: 25-1811888

Good Day Mr. Kelly:

My colleague, Dr. Robert (Bob) Golden, and I would like to schedule some time soon to have a Conference Call with you. We want you to clearly understand our Goals and Objectives as well as the importance and purpose of our soon to be completed peer-reviewed Science Committee Report.

Toward this end, I am attaching my PowerPoint Presentation. Bob and I each realize that slides 7 through 11 as being the most important because they visually depict the distortive effects of the LNT sharply contrasted with (and compared to) science-based data points. As you are aware, even now and through time, the former EPA Administrator, Gina McCarthy, consistently and emphatically repeats in interviews as well as in testimony over four years ago (on November 14, 2013), before the US House of Representatives Committee on Science, Space and Technology, she testified:

> "...Let me begin by stating that science is and has always been the backbone of the EPA's decision-making. The Agency's ability to pursue its mission to protect human health and the environment depends upon the integrity of the science upon which it relies. I firmly believe that environmental policies, decisions, guidance, and regulations that impact the lives of all Americans must be grounded, at a most fundamental level, in sound, high quality, transparent, science..."
> (https://science.house.gov/sites/republicans.science.house.gov/files/documents/HHRG-113-SY-20131114-SD001%20.pdf as well as http://www.c-span.org/video/?327016-1/epa-administrator-gina-mccarthy-testimony-proposed-regulations

As you know, the Goal of this project is to determine, through a rigorous analyses of both the radiation and chemical data, the comparative validity of the science. The ***CTC Foundation's*** Science Committee that will compare and contrast the scientific evidence for the LNT and threshold models for radiation- and chemical-induced cancer and non-cancer effects in humans. This Committee was empaneled in October, 2016 and is comprised of recognized experts, from diverse disciplines and backgrounds. Their purpose is to develop a comprehensive peer-reviewed publication. Bob Golden and Dr. Edward Calabrese (https://www.umass.edu/sphhs/person/faculty/edward-j-calabrese) are Co-Chairs of the Science Committee.

We look forward to our Conference Call as soon as possible. We are very grateful for your time, attention and assistance – Thank You.

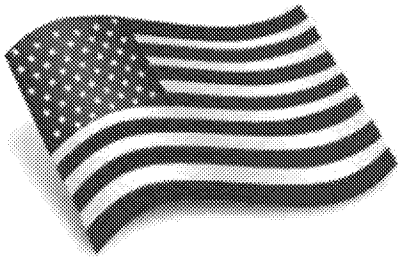
Most sincerely yours,

*Howard*

Howard G. McClintic

Executive Director

**Ex. 6 Personal Privacy (PP)**



This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

www.ctc.com 1-800-282-4392

This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

www.ctc.com 1-800-282-4392

Message

**From**: Konkus, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=555471B2BAA6419E8E141696F4577062-KONKUS, JOH]
**Sent**: 2/19/2019 4:12:30 PM
**To**: Knickmeyer, Ellen [EKnickmeyer@ap.org]
**Subject**: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Ellen: This conversations: "And when you all said you don't know why the EPA's press release quoted Calabrese on the rule – that was false, right?" Was off the record and remains so, I was telling you I personally didn't know why.

---

**From:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Sent:** Tuesday, February 19, 2019 11:02 AM
**To:** Konkus, John <konkus.john@epa.gov>; Feldman, Carole <CFeldman@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>; Block, Molly <block.molly@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, John. I saw the LA Times story today saying Calabrese wrote that portion of the EPA rule.

So the answer to my question here last October was a yes, correct?

And when you all said you don't know why the EPA's press release quoted Calabrese on the rule – that was false, right?

Thanks,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Monday, October 01, 2018 1:33 PM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, John,
On the part of the Transparency rule that deals with dose-response for radiation and chemicals, and says regulators should consider alternate theories in addition to LNT, did Edward Calabrese and or Steven Milloy play a role in crafting it?
Best,
Ellen

---

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Friday, September 14, 2018 10:53 AM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>

**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

The Radiation Health Effects site reflects recent information and was last updated in July 2018.

EPA's proposed rule on Strengthening Transparency in Regulatory Science did not discuss radiation. The Agency did seek comment on increasing transparency of the assumptions underlying dose response models. As noted previously, the timeline for any future action on this proposal has not yet been determined and EPA is reviewing more than 500,000 comments.

EPA continues to use the linear-no-threshold model for population-level radiation protection purposes. The EPA's Radiation Protection Program acknowledges uncertainty regarding health effects at low doses and is supportive of continued research in this area. More information in support of this approach can be found in the International Commission on Radiological Protection Report 103 and the 2018 National Council on Radiation Protection and Measurements Commentary 27.

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Friday, September 14, 2018 8:34 AM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thank you.

Sent from my iPhone

On Sep 14, 2018, at 8:30 AM, Konkus, John <konkus.john@epa.gov> wrote:

> Ellen: We're working on something more robust for you. Should have it this morning.
>
> John
>
> Sent from my iPhone
>
> On Sep 14, 2018, at 5:52 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
>> Hi, Enesta,
>>
>> That EPA website entry you sent me a link to seems to be a contradictory statements saying exposures below 10 rem usually have no harmful health effects but the EPA still follows the guideline that no exposure is safe.
>>
>> When does that entry date from? When was it revised and what part was revised?
>>
>> Your other statement provides no information at all, except to indicate the EPA may decide to reverse its longstanding policy on radiation exposure without any advance notice to the public it is considering doing that.
>>
>> Can you answer my questions and provide an EPA expert to speak to? These are non-answers and public silence on important public health questions for Americans.

Best,
Ellen

Sent from my iPhone

On Sep 13, 2018, at 6:01 PM, Jones, Enesta <Jones.Enesta@epa.gov> wrote:

> Ellen,
> I inadvertently cut off the end of our response. Here it is:
>
> Find more information here: https://www.epa.gov/radiation/radiation-health-effects
>
> Ellen,
>
> "EPA is currently reviewing the more than 590,000 comments on the Strengthening Transparency in Regulatory Sciences proposal. The EPA will determine a timeline for a decision after it has more fully assessed the comments." — **EPA spokesperson**
>
> On Sep 13, 2018, at 10:32 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
> Hello – wanted to also ask, is this still EPA policy?
> https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
> "Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."
>
> "Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."
>
> Best,
> Ellen
>
> ---
>
> **From:** Knickmeyer, Ellen
> **Sent:** Thursday, September 13, 2018 10:06 AM
> **To:** 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>
> **Cc:** 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
> **Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards
>
> Hi, all,

I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer

Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From:** Konkus, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=555471B2BAA6419E8E141696F4577062-KONKUS, JOH]
**Sent:** 2/16/2019 8:38:42 PM
**To:** Woods, Clint [woods.clint@epa.gov]
**Subject:** Fwd: Story on Calabrese

Begin forwarded message:

**From:** "Block, Molly" <block.molly@epa.gov>
**Date:** February 16, 2019 at 12:23:09 PM EST
**To:** "Abboud, Michael" <abboud.michael@epa.gov>
**Cc:** "Hewitt, James" <hewitt.james@epa.gov>, "Konkus, John" <konkus.john@epa.gov>, "McFaul, Jessica" <mcfaul.jessica@epa.gov>
**Subject: Re: Story on Calabrese**

Here's the back and forth from 2/5

OK. Thanks.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Tuesday, February 5, 2019 1:27 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

EXTERNAL SOURCE
Hi Susanne –

On background: That's not true. The Agency did not approach him twice to direct ORD nor did he turn down an invitation to meet about serving in some capacity at EPA.

EPA has a number of advisory boards and science panels that he came in to talk about that. He was actually recommended to a number of employees at the Agency.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Tuesday, February 5, 2019 4:02 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi Molly,

Sorry about the long break, there. I'm back on the story.
Couple things I'd like to verify:

Ed Calabrese said he'd been approached twice by the EPA to direct ORD. He said he turned down the invitation both times. Once in Jan 2017, the next time was in June or July of 2017. Can you confirm or dispute this?
Thanks,
Susanne Rust

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 12:38 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

As we've previously stated: You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on these issues, and EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:16 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 11:15:28 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

I should have something for you shortly.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 2:13 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

Would it be fair to say the EPA declined to comment on Milloy and Calabrese's influence on the proposed ruling? Or will you have a response.
Thank you.
Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 7:24:49 AM

**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi,

I have information suggesting that Steve Milloy and Edward Calabrese were instrumental in crafting the ruling's suggestion to incorporate risk models other than LNT.
I wonder if you could tell me what their role was in crafting the rule and and who solicited their input?
Thank you.
Susanne

---

**From:** Rust, Susanne
**Sent:** Thursday, November 8, 2018 6:27:41 AM
**To:** Block, Molly
**Cc:** Press
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Understood. Still wondering when a final ruling or decision is expected?

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Thursday, November 8, 2018 6:27:01 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

As we've stated before, we are currently reviewing 590,000 public comments on the proposal.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Thursday, November 8, 2018 9:26 AM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi -

Any idea when the EPA will make a decision or submit a final ruling?
Thank you.

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 1:14:50 PM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

This should be helpful for you:

The proposed regulation takes comment on ensuring transparency and consideration of high quality studies evaluating models and model assumptions, including high quality studies that

examine different potential dose-response relationships. You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on particular studies, and the EPA is currently reviewing all of those comments to ensure the best proposal is put forward.

---

**From:** Rust, Susanne <susanne.rust@latimes.com>
**Sent:** Wednesday, November 7, 2018 3:18 PM
**To:** Block, Molly <block.molly@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Strengthening Transparency in Regulatory Science/ Media request

Hi

Ha. No. I'm not suggesting any new models. Just wondering what this is based on and why it's being incorporated? There's a discussion in the ruling about doubts re linearity non threshold models, and I'm curious about it's origin and why it's included in a ruling that seems to be mostly about transparency and open data? And what this would mean for the way EPA evaluates an performs risk assessments?
Thanks. Susanne

---

**From:** Block, Molly <block.molly@epa.gov>
**Sent:** Wednesday, November 7, 2018 11:58 AM
**To:** Rust, Susanne
**Cc:** Press
**Subject:** RE: Strengthening Transparency in Regulatory Science/ Media request

Susanne –

Do you have specific questions? Or are you interested in any specific models? The transparency rule does not ask for the public to suggest or otherwise comment on "new models to evaluate risk assessment."

I'm happy to help, just trying to figure out the best way to answer your inquiry.

Molly

Begin forwarded message:

> **From:** "Rust, Susanne" <susanne.rust@latimes.com>
> **Date:** November 7, 2018 at 8:37:03 AM EST
> **To:** "daguillard.robert@epa.gov" <daguillard.robert@epa.gov>
> **Subject: Strengthening Transparency in Regulatory Science/ Media request**
>
> Dear Mr. Daguillard,
>
> I am working on a story about the "Strengthening Transparency in Regulatory Science" proposal and I am hoping I can get some information and maybe a comment?

I am particularly interested in the proposed rule's request for new models to evaluate risk assessment.
Any chance you can talk today? Or can you put me in touch with someone who can tell me how this came about and why? My deadline is tomorrow at noon.
Thank you.
Susanne Rust

Reporter, Los Angeles Times
650-804-6790

Sent from my iPhone

On Feb 16, 2019, at 11:08 AM, Abboud, Michael <abboud.michael@epa.gov> wrote:

Oh yeah she already sent her over answers.

Sent from my iPhone

On Feb 16, 2019, at 12:04 PM, Hewitt, James <hewitt.james@epa.gov> wrote:

No idea. Molly had worked with an LA Times reporter on something else.

Sent from my iPhone

On Feb 16, 2019, at 11:54 AM, Abboud, Michael <abboud.michael@epa.gov> wrote:

Did we already provide statements on this?

Sent from my iPhone

Begin forwarded message:

**From:** "Woods, Clint" <woods.clint@epa.gov>
**Date:** February 16, 2019 at 11:14:10 AM EST
**To:** "Konkus, John" <konkus.john@epa.gov>, "Abboud, Michael" <abboud.michael@epa.gov>
**Subject: Fwd: Story on Calabrese**

Begin forwarded message:

**From:** "Rust, Susanne" <susanne.rust@latimes.com>
**Date:** February 16, 2019 at 8:58:17 AM EST
**To:** "Woods, Clint" <woods.clint@epa.gov>
**Subject: Story on Calabrese**

HI,

I wanted to let you know the story I contacted you about several weeks ago is slated to run tomorrow.
I'll send a link when it goes live.
THanks, Susanne

Reporter, The Los Angeles Times
650-804-6790

Message

**From**: Konkus, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=555471B2BAA6419E8E141696F4577062-KONKUS, JOH]
**Sent**: 10/4/2018 1:58:43 PM
**To**: Knickmeyer, Ellen [EKnickmeyer@ap.org]; Press [Press@epa.gov]
**CC**: Feldman, Carole [CFeldman@ap.org]
**Subject**: RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Ellen:

"The proposed regulation takes comment on ensuring transparency and consideration of high quality studies evaluating models and model assumptions, including high quality studies that examine different potential dose-response relationships – the list below is literally a description of every potential shape of a curve. You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on particular studies, and the EPA is currently reviewing all of those comments to ensure the best proposal is put forward." – EPA Spokesperson

Also, you mistakenly list Dr. Calabrese as an "EPA Expert." He is not affiliated with EPA. The hearing yesterday was a Congressional hearing not an EPA hearing. EPA did not present at the hearing.

Thank you,

John Konkus

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, October 4, 2018 7:38 AM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Cc:** Feldman, Carole <CFeldman@ap.org>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Hi, John,
Can you please explain what the reference to J and U shaped models means in the proposed regulation. It's very specific language, it's in the proposal for a regulation, what does it mean?

EPA proposal:
'The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies that explore: A broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models.'"

Below are four explanations from experts of all ranges of opinion on the EPA proposal, all saying the U and J shaped model is Calabrese's hormesis model, meaning the model for the theory that exposure to a hazardous substance is beneficial at lower doses.

If that isn't what it means, what does it mean? All you're saying to these expert assessments is "Nope."

EPA'S EXPERT:
Edward Calabrese:
"Enter an alternative model, which claims that the fundamental shape of the dose–response curve is neither linear nor threshold, but rather U-shaped. This so-called hormesis model—after the Greek word 'to excite'—was first applied to describe dose–response relationships by Southam & Ehrlich (1943) more than 60 years ago. A typical hormetic curve is either Ushaped or has an inverted U-shaped dose–response, depending on the endpoint measured. If the endpoint is growth or longevity, the dose–response would be that of an inverted U-shape; if the endpoint is disease incidence, then the dose–response would be described as U- or J-shaped (Fig 1). "
Calabrese says this rule as it reads would apply to radiation and chemicals.

2nd expert:
Marco Kaltofen, PhD, PE (Civil, MA), C. NSE Affiliate Research Engineer
Nuclear Science and Engineering Program, Dept. of Physics, Worcester Polytechnic Institute
"EPA has used a straight line model. That means more poison equals more harm. 500 hundred years of scientific data supports this model.Now
EPA wants to use a squiggly model. That means that a little poison might be good for you, so let's try it. EPA calls it a J-model because harm goes down first, then goes up, like a J shape.

---
3rd expert:
Jennifer Sass, Ph.D.
Senior Scientist, Natural Resources Defense Council
Part-time faculty, George Washington University
Linear no-threshold: "The idea is that any amount of exposure is associated with some amount of risk. The higher the exposure, the higher the risk. The only time you're going to have zero risk is when you have zero exposure."
"What this (EPA proposal) is trying to pretend is that EPA's models are uncertain as if they had a problem and somehow these other models are better....J or U shape."
Sasse says this rule as it reads would apply to radiation and chemicals.

4th expert:
John Peterson Myers
Environmental Health Sciences
609 East High St
Charlottesville VA 22902
Calabrese bases his arguments on widespread occurrence of 'hormetic' responses in the literature. A 'hormetic' response is a special case of a larger set of dose-response curves called 'non-monotonic dose response curves' (NMDRCs), named thus because the slope of the curve changes sign somewhere along the curve (a term out of mathematics). Hence a J-shaped or U-shaped or inverted-U shaped curve are all non-monotonic.

---

**From:** Abboud, Michael <abboud.michael@epa.gov>
**Sent:** Wednesday, October 03, 2018 5:13 PM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>; Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Please see below.

"The proposed rule does not refer to cancer-causing agents or hormesis. It stated: 'The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies

that explore: A broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models.'" **– EPA spokesman**

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Wednesday, October 3, 2018 4:25 PM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Hi, John,
Dr. Calabrese just now and the independent physicists I talked to said that the J and U shaped models that the EPA proposal cites refers only to hormesis, which is the idea that cancer-causing agents are actually beneficial at lower doses.

Can you comment on that, specifically? Would the proposal require regulators to consider that hazardous substances at low doses are healthy, and if not, what does the reference to U and J shaped models mean?
Thanks,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Wednesday, October 03, 2018 8:25 AM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Subject:** Questions on risk models and EPA's proposal on scientific studies

(Sent a few minutes ago but it looks like it may have hung up in my email – repeating again just in case.)

Hi, John.
I'm sure we will be writing more on the EPA's proposal on scientific studies and wanted to nail down a couple points from the proposal. Please bear with me, because this is technical, and we have to be able to phrase it for readers in the simplest way possible.

One question – the EPA proposal says there is "growing empirical evidence of non-linearity in the concentration response function for specific pollutants and health effects."

Can you please send along and specify what studies, pollutants, and health effects are being cited there?

Second question – the EPA proposal below says in considering risks of low doses the EPA should look not just at linear models, but threshold, U-shaped, and bell-shaped models, and consider "model uncertainty" as a default.

The physics academics I talk to, and Dr. Calabrese in his writing, say U-shaped and J-shaped curves apply only to models showing beneficial effects from lower doses of harmful

substances, or the "hormesis" that Calabrese writes about for radiation and toxins. Can you confirm that, or if not what does that refer to, specifically?

EPA Proposal:
In addition, this proposed regulation is designed to increase transparency of the assumptions underlying dose response models. As a case in point, there is growing empirical evidence of non-linearity in the concentrationresponse function for specific pollutants and health effects. The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies that explore: A broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, Jshaped, and bell-shaped models.

Calabrese on "hormesis" in radiation and chemicals:
Enter an alternative model, which claims that the fundamental shape of the dose–response curve is neither linear nor threshold, but rather U-shaped. This so-called hormesis model—after the Greek word 'to excite'—was first applied to describe dose–response relationships by Southam & Ehrlich (1943) more than 60 years ago. A typical hormetic curve is either Ushaped or has an inverted U-shaped dose–response, depending on the endpoint measured. If the endpoint is growth or longevity, the dose–response would be that of an inverted U-shape; if the endpoint is disease incidence, then the dose–response would be described as U- or J-shaped (Fig 1).

Thank you,
Ellen

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.

Message

**From**: Konkus, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=555471B2BAA6419E8E141696F4577062-KONKUS, JOH]
**Sent**: 11/21/2018 1:16:32 PM
**To**: Sauerhage, Maggie [Sauerhage.Maggie@epa.gov]
**CC**: Press [Press@epa.gov]
**Subject**: Re: Ed Calabrese

We will thx

John Konkus
Environmental Protection Agency
Deputy Associate Administrator
Office of Public Affairs

On Nov 21, 2018, at 8:14 AM, Sauerhage, Maggie <Sauerhage.Maggie@epa.gov> wrote:

> Will third floor handle?
>
> Maggie Sauerhage
> Office of Public Affairs
> U.S. Environmental Protection Agency
> Office: (202) 564-0443
> Cell: Ex. 6 Personal Privacy (PP)
>
> ---
>
> **From:** Woods, Clint
> **Sent:** Wednesday, November 21, 2018 7:35 AM
> **To:** Rust, Susanne <susanne.rust@latimes.com>
> **Cc:** Press <Press@epa.gov>
> **Subject:** Re: Ed Calabrese
>
> Ms. Rust,
>
> Thanks so much for your email - Our press team will be in touch.
>
> Clint
>
> On Nov 20, 2018, at 12:33 PM, Rust, Susanne <susanne.rust@latimes.com> wrote:
>
>> Dear Mr Woods,
>>
>> I'm a reporter at the Los Angeles Times working on a story about hormesis, Ed Calabrese, LNT and the EPA's proposed new rule on transparency in science.
>> I came across some emails you exchanged with Dr. Calabrese this spring about LNT. According to the chronology, you sought Calabrese's advice on what to incorporate into the rule, you spoke, and he also provided you with language to use, which was then incorporated into the rule - word-for-word.
>> I wonder if you could answer some questions about this exchange for me?
>>
>> 1) Who suggested you contact Calabrese?
>> 2) What other toxicologists/scientists did you consult with?

3) In one of your emails, you mentioned that you and Calabrese had known one another years ago. Can you tell me how?

Thanks for your time. Feel free to call me at: 650-804-6790.

Susanne Rust

Reporter, The Los Angeles Times

Ex. 6 Personal Privacy (PP)

Message

**From**: Konkus, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=555471B2BAA6419E8E141696F4577062-KONKUS, JOH]
**Sent**: 10/2/2018 8:05:17 PM
**To**: cfeldman@ap.org; Knickmeyer, Ellen [EKnickmeyer@ap.org]
**CC**: Press [Press@epa.gov]
**Subject**: FW: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

**Importance**: High

Here's the statement we sent and we're standing by. Thank you for taking the time to talk through this.

---

**From:** Konkus, John
**Sent:** Friday, September 14, 2018 10:53 AM
**To:** 'Knickmeyer, Ellen' <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

The Radiation Health Effects site reflects recent information and was last updated in July 2018.

EPA's proposed rule on Strengthening Transparency in Regulatory Science did not discuss radiation. The Agency did seek comment on increasing transparency of the assumptions underlying dose response models. As noted previously, the timeline for any future action on this proposal has not yet been determined and EPA is reviewing more than 500,000 comments.

EPA continues to use the linear-no-threshold model for population-level radiation protection purposes. The EPA's Radiation Protection Program acknowledges uncertainty regarding health effects at low doses and is supportive of continued research in this area. More information in support of this approach can be found in the International Commission on Radiological Protection Report 103 and the 2018 National Council on Radiation Protection and Measurements Commentary 27.

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Friday, September 14, 2018 8:34 AM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thank you.

Sent from my iPhone

On Sep 14, 2018, at 8:30 AM, Konkus, John <konkus.john@epa.gov> wrote:

> Ellen: We're working on something more robust for you. Should have it this morning.
>
> John

Sent from my iPhone

On Sep 14, 2018, at 5:52 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:

> Hi, Enesta,
>
> That EPA website entry you sent me a link to seems to be a contradictory statements saying exposures below 10 rem usually have no harmful health effects but the EPA still follows the guideline that no exposure is safe.
>
> When does that entry date from? When was it revised and what part was revised?
>
> Your other statement provides no information at all, except to indicate the EPA may decide to reverse its longstanding policy on radiation exposure without any advance notice to the public it is considering doing that.
>
> Can you answer my questions and provide an EPA expert to speak to? These are non-answers and public silence on important public health questions for Americans.
>
> Best,
> Ellen
>
> Sent from my iPhone
>
> On Sep 13, 2018, at 6:01 PM, Jones, Enesta <Jones.Enesta@epa.gov> wrote:
>
>> Ellen,
>> I inadvertently cut off the end of our response. Here it is:
>>
>> Find more information here: https://www.epa.gov/radiation/radiation-health-effects
>>
>> Ellen,
>>
>> "EPA is currently reviewing the more than 590,000 comments on the Strengthening Transparency in Regulatory Sciences proposal. The EPA will determine a timeline for a decision after it has more fully assessed the comments." — **EPA spokesperson**
>>
>> On Sep 13, 2018, at 10:32 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>>
>> Hello – wanted to also ask, is this still EPA policy?
>> https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
>> "Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."
>>
>> "Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the

conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."

Best,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>
**Cc:** 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org

Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From**: Konkus, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=555471B2BAA6419E8E141696F4577062-KONKUS, JOH]
**Sent**: 10/2/2018 6:16:59 PM
**To**: Knickmeyer, Ellen [EKnickmeyer@ap.org]; cfeldman@ap.org; jpace@ap.org
**CC**: Press [Press@epa.gov]
**Subject**: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

**Importance**: High

Adding AP editors.

---

**From:** Konkus, John
**Sent:** Tuesday, October 2, 2018 2:04 PM
**To:** 'Knickmeyer, Ellen' <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards
**Importance:** High

Ellen: Your article frames this issue as a "radiation regulation" but we told you in our statement (see below) that this proposed rule "did not discuss radiation." There is no "radiation regulation" as you put it. Please retract your article before other outlets follow this mistake.

Also the strengthening transparency in science comment period has already closed.

---

**From:** Konkus, John
**Sent:** Friday, September 14, 2018 10:53 AM
**To:** 'Knickmeyer, Ellen' <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

The Radiation Health Effects site reflects recent information and was last updated in July 2018.

EPA's proposed rule on Strengthening Transparency in Regulatory Science did not discuss radiation. The Agency did seek comment on increasing transparency of the assumptions underlying dose response models. As noted previously, the timeline for any future action on this proposal has not yet been determined and EPA is reviewing more than 500,000 comments.

EPA continues to use the linear-no-threshold model for population-level radiation protection purposes. The EPA's Radiation Protection Program acknowledges uncertainty regarding health effects at low doses and is supportive of continued research in this area. More information in support of this approach can be found in the International Commission on Radiological Protection Report 103 and the 2018 National Council on Radiation Protection and Measurements Commentary 27.

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Friday, September 14, 2018 8:34 AM
**To:** Konkus, John <konkus.john@epa.gov>

**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thank you.

Sent from my iPhone

On Sep 14, 2018, at 8:30 AM, Konkus, John <konkus.john@epa.gov> wrote:

> Ellen: We're working on something more robust for you. Should have it this morning.
>
> John
>
> Sent from my iPhone
>
> On Sep 14, 2018, at 5:52 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
>> Hi, Enesta,
>>
>> That EPA website entry you sent me a link to seems to be a contradictory statements saying exposures below 10 rem usually have no harmful health effects but the EPA still follows the guideline that no exposure is safe.
>>
>> When does that entry date from? When was it revised and what part was revised?
>>
>> Your other statement provides no information at all, except to indicate the EPA may decide to reverse its longstanding policy on radiation exposure without any advance notice to the public it is considering doing that.
>>
>> Can you answer my questions and provide an EPA expert to speak to? These are non-answers and public silence on important public health questions for Americans.
>>
>> Best,
>> Ellen
>>
>> Sent from my iPhone
>>
>> On Sep 13, 2018, at 6:01 PM, Jones, Enesta <Jones.Enesta@epa.gov> wrote:
>>
>>> Ellen,
>>> I inadvertently cut off the end of our response. Here it is:
>>>
>>> Find more information here: https://www.epa.gov/radiation/radiation-health-effects
>>>
>>> Ellen,
>>>
>>> "EPA is currently reviewing the more than 590,000 comments on the Strengthening Transparency in Regulatory Sciences proposal. The EPA will determine a timeline for a decision after it has more fully assessed the comments." — **EPA spokesperson**

On Sep 13, 2018, at 10:32 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:

Hello – wanted to also ask, is this still EPA policy?
https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
"Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."

"Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."

Best,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>
**Cc:** 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From**: Konkus, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=555471B2BAA6419E8E141696F4577062-KONKUS, JOH]
**Sent**: 10/3/2018 3:37:56 PM
**To**: Zahra Hirji [zahra.hirji@buzzfeed.com]
**CC**: Press [Press@epa.gov]
**Subject**: RE: Media Request: Question About Science Transparency Rule & Radiation Guidelines

You can attribute that statement to me.

On your second question, the answer is no Population-level radiation protection just refers to EPA's role in radiation protection (https://www.epa.gov/radiation/epas-role-radiation-protection)

**From:** Zahra Hirji [mailto:zahra.hirji@buzzfeed.com]
**Sent:** Wednesday, October 3, 2018 11:06 AM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Press <Press@epa.gov>
**Subject:** Re: Media Request: Question About Science Transparency Rule & Radiation Guidelines

Hi John,

Thanks so much for this comment. I have two follow ups. Can I attribute this quote to you -- it seems the AP article does, and I'm curious why it was provided to me on background.

Second, you say "EPA's policy is to continue to use the linear-no-threshold model for population-level radiation protection purposes" -- but what about using the model for individual-level radiation protection purposes? My understanding is there are times when the EPA sets a protection radiation or contamination standard based on the individual with the highest risk, say for a community near a Superfund site. Are you saying the rule change leaves the door open for changing individual-level radiation protection purpose -- or not?

Thanks,
Zahra

On Wed, Oct 3, 2018 at 8:17 AM Konkus, John <konkus.john@epa.gov> wrote:

> "The proposed regulation doesn't talk about radiation or any particular chemicals. EPA's policy is to continue to use the linear-no-threshold model for population-level radiation protection purposes which would not – under the proposed regulation that has not been finalized – trigger any change in that policy." - - EPA Spokesperson
>
> The extended comment period has closed. We received over 590,000 comments.

On Oct 3, 2018, at 8:04 AM, Zahra Hirji <zahra.hirji@buzzfeed.com> wrote:

> Dear John Konkus,
>
> I'm a reporter for BuzzFeed News covering EPA's science transparency rule, and I have a few questions about the impacts. Yesterday, the AP published a story suggesting the rule proposal could impact EPA's radiation guidelines. While it's true the rule proposal does not mention radiation or the guidelines specifically, it does mention opening the discussion on various models. (Here's a sentence from the docket page for the rule: "EPA shall evaluate the appropriateness of using default assumptions,

including assumptions of a linear, no-threshold dose response, on a case-by-case basis.") Some scientists I've spoken to say it is possible reconsidering the linear non-threshold model and the radiation guidelines could be impacted by the larger rule proposal, even though it's not spelled out so clearly in the proposal -- and it appears some people have provided comments to the proposal on this subject.

Can you confirm the public comment period on the rule proposal asked for input on the types of models that dictate the EPA's radiation guidelines and could open the door to changing these guidelines down the road? And can you comment on why University of Massachusetts scientist Edward Calabrese is quoted in EPA's press release for the rule saying essentially just that?

I am on deadline, and am looking to publish a story ahead of today's Senate EPW hearing on the transparency rule (where Calabrese is one of three invited speakers) and available on my cell at Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)

Best,
Zahra Hirji

--
Zahra Hirji
Reporter
BuzzFeed News
Office Ex. 6 Personal Privacy (PP)
Cell: (
Zahra.Hirji@buzzfeed.com
@zhirji28

--
Zahra Hirji
Reporter
BuzzFeed News
Offi Ex. 6 Personal Privacy (PP)
Cell
Zahra.Hirji@buzzfeed.com
@zhirji28

Message

**From**: Konkus, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=555471B2BAA6419E8E141696F4577062-KONKUS, JOH]
**Sent**: 10/4/2018 3:15:15 PM
**To**: Knickmeyer, Ellen [EKnickmeyer@ap.org]; Press [Press@epa.gov]
**CC**: Feldman, Carole [CFeldman@ap.org]
**Subject**: RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

"The list of shapes in the proposal is a description of virtually every potential shape of a curve in a dose-response relationship." – EPA Spokesperson

Dr. Calabrese is not affiliated with EPA.

The proposed rule did not refer to hormesis.

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, October 4, 2018 11:10 AM
**To:** Konkus, John <konkus.john@epa.gov>; Press <Press@epa.gov>
**Cc:** Feldman, Carole <CFeldman@ap.org>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Hi, John.

Sorry, the email yesterday cited Michael only.

Can you ask Clint for the specific meaning of the U and J curves in the proposed regulation? In risk assessment they are used to describe Dr. Calabrese's theory of hormesis, which is the theory that hazardous substances at lower doses are good for you.

Is hormesis one of the models that the proposal says the agency should consider?

If the U and J shaped curves in the proposed regulation don't refer to hormesis, what do they refer to?

It's a straightforward questions about a pending regulation. The language would have an impact in the regulation, and the agency ought to be able to explain it.

Best
Ellen

---

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Thursday, October 04, 2018 10:39 AM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>; Press <Press@epa.gov>
**Cc:** Feldman, Carole <CFeldman@ap.org>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Ellen,

We refer you to our previous statement: "The list of shapes in the proposal is a description of virtually every potential shape of a curve in a dose-response relationship." – EPA Spokesperson

Finally, you wrote "Michael told me yesterday…" It was not Michael who told you that, it was Clint Woods, the EPA Deputy Associate Administrator for the Office of Air and Radiation.

Thank you,

John

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, October 4, 2018 10:25 AM
**To:** Konkus, John <konkus.john@epa.gov>; Press <Press@epa.gov>
**Cc:** Feldman, Carole <CFeldman@ap.org>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Hi, John. The published literature on risk assessment and the specialists I talked to in risk assessment say the U and J curve in risk-assessment refer only to hormesis, or Dr. Calabrese's theory that hazardous substances are good for you at lower doses.
Michael told me yesterday when I asked about the J and U curves that hormesis is not in the proposal. What do the J and U curves in the proposed regulation refer to, then?
Thanks.
Ellen

---

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Thursday, October 04, 2018 10:20 AM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>; Press <Press@epa.gov>
**Cc:** Feldman, Carole <CFeldman@ap.org>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

"The list of shapes in the proposal is a description of virtually every potential shape of a curve in a dose-response relationship." – EPA Spokesperson

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, October 4, 2018 10:02 AM
**To:** Konkus, John <konkus.john@epa.gov>; Press <Press@epa.gov>
**Cc:** Feldman, Carole <CFeldman@ap.org>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

What does the U and J shaped model mean in the proposal?

---

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Thursday, October 04, 2018 9:59 AM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>; Press <Press@epa.gov>
**Cc:** Feldman, Carole <CFeldman@ap.org>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Ellen:

"The proposed regulation takes comment on ensuring transparency and consideration of high quality studies evaluating models and model assumptions, including high quality studies that examine different potential dose-response relationships – the list below is literally a description of every potential shape of a curve. You need look no further than the 590,000 public comments provided to EPA on this proposal to see literally thousands of different viewpoints on

particular studies, and the EPA is currently reviewing all of those comments to ensure the best proposal is put forward." – EPA Spokesperson

Also, you mistakenly list Dr. Calabrese as an "EPA Expert." He is not affiliated with EPA. The hearing yesterday was a Congressional hearing not an EPA hearing. EPA did not present at the hearing.

Thank you,

John Konkus

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, October 4, 2018 7:38 AM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Cc:** Feldman, Carole <CFeldman@ap.org>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Hi, John,
Can you please explain what the reference to J and U shaped models means in the proposed regulation. It's very specific language, it's in the proposal for a regulation, what does it mean?

EPA proposal:
'The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies that explore: A broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models.'"

Below are four explanations from experts of all ranges of opinion on the EPA proposal, all saying the U and J shaped model is Calabrese's hormesis model, meaning the model for the theory that exposure to a hazardous substance is beneficial at lower doses.

If that isn't what it means, what does it mean? All you're saying to these expert assessments is "Nope."

EPA'S EXPERT:
Edward Calabrese:
"Enter an alternative model, which claims that the fundamental shape of the dose–response curve is neither linear nor threshold, but rather U-shaped. This so-called hormesis model—after the Greek word 'to excite'—was first applied to describe dose–response relationships by Southam & Ehrlich (1943) more than 60 years ago. A typical hormetic curve is either Ushaped or has an inverted U-shaped dose–response, depending on the endpoint measured. If the endpoint is growth or longevity, the dose–response would be that of an inverted U-shape; if the endpoint is disease incidence, then the dose–response would be described as U- or J-shaped (Fig 1). "
Calabrese says this rule as it reads would apply to radiation and chemicals.

2nd expert:
Marco Kaltofen, PhD, PE (Civil, MA), C. NSE Affiliate Research Engineer
Nuclear Science and Engineering Program, Dept. of Physics, Worcester Polytechnic Institute

"EPA has used a straight line model. That means more poison equals more harm. 500 hundred years of scientific data supports this model.Now
EPA wants to use a squiggly model. That means that a little poison might be good for you, so let's try it. EPA calls it a J-model because harm goes down first, then goes up, like a J shape.

---
3rd expert:
Jennifer Sass, Ph.D.
Senior Scientist, Natural Resources Defense Council
Part-time faculty, George Washington University
Linear no-threshold: "The idea is that any amount of exposure is associated with some amount of risk. The higher the exposure, the higher the risk. The only time you're going to have zero risk is when you have zero exposure."
"What this (EPA proposal) is trying to pretend is that EPA's models are uncertain as if they had a problem and somehow these other models are better....J or U shape."
Sasse says this rule as it reads would apply to radiation and chemicals.

4th expert:
John Peterson Myers
Environmental Health Sciences
609 East High St
Charlottesville VA 22902
Calabrese bases his arguments on widespread occurrence of 'hormetic' responses in the literature. A 'hormetic' response is a special case of a larger set of dose-response curves called 'non-monotonic dose response curves' (NMDRCs), named thus because the slope of the curve changes sign somewhere along the curve (a term out of mathematics). Hence a J-shaped or U-shaped or inverted-U shaped curve are all non-monotonic.

---

**From:** Abboud, Michael <abboud.michael@epa.gov>
**Sent:** Wednesday, October 03, 2018 5:13 PM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>; Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Please see below.

"The proposed rule does not refer to cancer-causing agents or hormesis. It stated: 'The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies that explore: A broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models.'" **– EPA spokesman**

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Wednesday, October 3, 2018 4:25 PM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Subject:** RE: Questions on risk models and EPA's proposal on scientific studies-on deadline

Hi, John,

Dr. Calabrese just now and the independent physicists I talked to said that the J and U shaped models that the EPA proposal cites refers only to hormesis, which is the idea that cancer-causing agents are actually beneficial at lower doses.

Can you comment on that, specifically? Would the proposal require regulators to consider that hazardous substances at low doses are healthy, and if not, what does the reference to U and J shaped models mean?
Thanks,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Wednesday, October 03, 2018 8:25 AM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Subject:** Questions on risk models and EPA's proposal on scientific studies

(Sent a few minutes ago but it looks like it may have hung up in my email – repeating again just in case.)

Hi, John.
I'm sure we will be writing more on the EPA's proposal on scientific studies and wanted to nail down a couple points from the proposal. Please bear with me, because this is technical, and we have to be able to phrase it for readers in the simplest way possible.

One question – the EPA proposal says there is "growing empirical evidence of non-linearity in the concentration response function for specific pollutants and health effects."

Can you please send along and specify what studies, pollutants, and health effects are being cited there?

Second question – the EPA proposal below says in considering risks of low doses the EPA should look not just at linear models, but threshold, U-shaped, and bell-shaped models, and consider "model uncertainty" as a default.

The physics academics I talk to, and Dr. Calabrese in his writing, say U-shaped and J-shaped curves apply only to models showing beneficial effects from lower doses of harmful substances, or the "hormesis" that Calabrese writes about for radiation and toxins. Can you confirm that, or if not what does that refer to, specifically?

EPA Proposal:
In addition, this proposed regulation is designed to increase transparency of the assumptions underlying dose response models. As a case in point, there is growing empirical evidence of non-linearity in the concentrationresponse function for specific pollutants and health effects. The use of default models, without consideration of alternatives or model uncertainty, can obscure the scientific justification for EPA actions. To be even more transparent about these complex relationships, EPA should give appropriate consideration to high quality studies that

explore: A broad class of parametric concentration-response models with a robust set of potential confounding variables; nonparametric models that incorporate fewer assumptions; various threshold models across the exposure range; and spatial heterogeneity. EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, Jshaped, and bell-shaped models.

Calabrese on "hormesis" in radiation and chemicals:
Enter an alternative model, which claims that the fundamental shape of the dose–response curve is neither linear nor threshold, but rather U-shaped. This so-called hormesis model—after the Greek word 'to excite'—was first applied to describe dose–response relationships by Southam & Ehrlich (1943) more than 60 years ago. A typical hormetic curve is either Ushaped or has an inverted U-shaped dose–response, depending on the endpoint measured. If the endpoint is growth or longevity, the dose–response would be that of an inverted U-shape; if the endpoint is disease incidence, then the dose–response would be described as U- or J-shaped (Fig 1).

Thank you,
Ellen

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.

Message

**From**: Stevens, Katherine [stevens.katherine@epa.gov]
**Sent**: 9/13/2018 6:53:33 PM
**To**: Lynn, Tricia [lynn.tricia@epa.gov]; Wieder, Jessica [Wieder.Jessica@epa.gov]; Millett, John [Millett.John@epa.gov]
**Subject**: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards
**Attachments**: LNT AP Inquiry 09132018.docx

Hey, Tricia,

RPD prefers to answer in writing.

See attached.

Thanks,
K

Kati Stevens
Public Affairs Specialist
Office of Air and Radiation
U.S. Environmental Protection Agency
Desk: (202)-564-3251

Please consider the environment before printing this e-mail

**From:** Lynn, Tricia
**Sent:** Thursday, September 13, 2018 10:58 AM
**To:** Wieder, Jessica <Wieder.Jessica@epa.gov>; Stevens, Katherine <stevens.katherine@epa.gov>; Millett, John <Millett.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thanks Jess. I received it too (with an additional question) and just sent it on to Katie.

She's requesting an interview. Up to y'all if you want to go that route or in writing, of course.

Best,

Tricia

**From:** Wieder, Jessica
**Sent:** Thursday, September 13, 2018 10:56 AM
**To:** Stevens, Katherine <stevens.katherine@epa.gov>; Millett, John <Millett.John@epa.gov>; Lynn, Tricia <lynn.tricia@epa.gov>
**Subject:** FW: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards
**Importance:** High

Hi Tricia, John and Kati,

We received an AP inquiry on our use of LNT in light of the proposed transparency rule (see below). We are drafting a response and will run it through our normal chain, up to OPA for review and response.

Jess

Jessica Wieder
Director, Center for Radiation Information and Outreach
U.S. Environmental Protection Agency
Radiation Protection Program
w: 202-343-9201
c: Ex. 6 Personal Privacy (PP)

---

**From:** Veal, Lee
**Sent:** Thursday, September 13, 2018 10:08 AM
**To:** Wieder, Jessica <Wieder.Jessica@epa.gov>; Boyd, Mike <Boyd.Mike@epa.gov>; DeCair, Sara <DeCair.Sara@epa.gov>
**Subject:** FW: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards
**Importance:** High

Lets chat today.

Lee Ann B. Veal
Director, Radiation Protection Division
Office of Radiation and Indoor Air
Office: 202-343-9448; Cell: Ex. 6 Personal Privacy (PP)
www.epa.gov/radiation

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Cc:** Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer

Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.

LNT AP Inquiry: September 13, 2018

Reporter:
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

**Inquiry:**

I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts: "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

Is this still EPA policy?
https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
"Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."

"Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."

**Proposed Answer**

# Ex. 5 Deliberative Process (DP)

Message

**From**: Millett, John [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=C067CAA6C93544F78C26AB08CC567D27-MILLETT, JOHN]
**Sent**: 10/1/2018 6:53:44 PM
**To**: Veal, Lee [Veal.Lee@epa.gov]; Stevens, Katherine [stevens.katherine@epa.gov]
**CC**: Wieder, Jessica [Wieder.Jessica@epa.gov]
**Subject**: Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thanks. Plus Katie

Sent from my iPhone

On Oct 1, 2018, at 2:31 PM, Veal, Lee <Veal.Lee@epa.gov> wrote:

No action, just an FYI

Lee Ann B. Veal
Director, Radiation Protection Division
Office of Radiation and Indoor Air
Office: 202-343-9448; Cell: Ex. 6 Personal Privacy (PP)
www.epa.gov/radiation

---

**From:** Konkus, John
**Sent:** Monday, October 01, 2018 2:06 PM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

"EPA received input from a number of stakeholders and utilized the intra and interagency process to ensure a robust proposal was put forward."

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Monday, October 1, 2018 1:33 PM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, John,
On the part of the Transparency rule that deals with dose-response for radiation and chemicals, and says regulators should consider alternate theories in addition to LNT, did Edward Calabrese and or Steven Milloy play a role in crafting it?
Best,
Ellen

---

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Friday, September 14, 2018 10:53 AM

**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

The Radiation Health Effects site reflects recent information and was last updated in July 2018.

EPA's proposed rule on Strengthening Transparency in Regulatory Science did not discuss radiation. The Agency did seek comment on increasing transparency of the assumptions underlying dose response models. As noted previously, the timeline for any future action on this proposal has not yet been determined and EPA is reviewing more than 500,000 comments.

EPA continues to use the linear-no-threshold model for population-level radiation protection purposes. The EPA's Radiation Protection Program acknowledges uncertainty regarding health effects at low doses and is supportive of continued research in this area. More information in support of this approach can be found in the International Commission on Radiological Protection Report 103 and the 2018 National Council on Radiation Protection and Measurements Commentary 27.

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Friday, September 14, 2018 8:34 AM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thank you.

Sent from my iPhone

On Sep 14, 2018, at 8:30 AM, Konkus, John <konkus.john@epa.gov> wrote:

> Ellen: We're working on something more robust for you. Should have it this morning.
>
> John
>
> Sent from my iPhone
>
> On Sep 14, 2018, at 5:52 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
>> Hi, Enesta,
>>
>> That EPA website entry you sent me a link to seems to be a contradictory statements saying exposures below 10 rem usually have no harmful health effects but the EPA still follows the guideline that no exposure is safe.
>>
>> When does that entry date from? When was it revised and what part was revised?
>>
>> Your other statement provides no information at all, except to indicate the EPA may decide to reverse its longstanding policy on radiation

exposure without any advance notice to the public it is considering doing that.

Can you answer my questions and provide an EPA expert to speak to? These are non-answers and public silence on important public health questions for Americans.

Best,
Ellen

Sent from my iPhone

On Sep 13, 2018, at 6:01 PM, Jones, Enesta <Jones.Enesta@epa.gov> wrote:

> Ellen,
> I inadvertently cut off the end of our response. Here it is:
>
> Find more information here: https://www.epa.gov/radiation/radiation-health-effects
>
> Ellen,
>
> "EPA is currently reviewing the more than 590,000 comments on the Strengthening Transparency in Regulatory Sciences proposal. The EPA will determine a timeline for a decision after it has more fully assessed the comments." — **EPA spokesperson**
>
> On Sep 13, 2018, at 10:32 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
> Hello – wanted to also ask, is this still EPA policy?
> https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
> "Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."
>
> "Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."
>
> Best,

Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>
**Cc:** 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)

Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.
The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From**: Konkus, John [konkus.john@epa.gov]
**Sent**: 10/1/2018 6:05:35 PM
**To**: Knickmeyer, Ellen [EKnickmeyer@ap.org]
**CC**: Jones, Enesta [Jones.Enesta@epa.gov]; Press [Press@epa.gov]; Edwards, Jonathan [Edwards.Jonathan@epa.gov]; Veal, Lee [Veal.Lee@epa.gov]; Griggs, John [Griggs.John@epa.gov]
**Subject**: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

"EPA received input from a number of stakeholders and utilized the intra and interagency process to ensure a robust proposal was put forward."

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Monday, October 1, 2018 1:33 PM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, John,
On the part of the Transparency rule that deals with dose-response for radiation and chemicals, and says regulators should consider alternate theories in addition to LNT, did Edward Calabrese and or Steven Milloy play a role in crafting it?
Best,
Ellen

---

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Friday, September 14, 2018 10:53 AM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

The Radiation Health Effects site reflects recent information and was last updated in July 2018.

EPA's proposed rule on Strengthening Transparency in Regulatory Science did not discuss radiation. The Agency did seek comment on increasing transparency of the assumptions underlying dose response models. As noted previously, the timeline for any future action on this proposal has not yet been determined and EPA is reviewing more than 500,000 comments.

EPA continues to use the linear-no-threshold model for population-level radiation protection purposes. The EPA's Radiation Protection Program acknowledges uncertainty regarding health effects at low doses and is supportive of continued research in this area. More information in support of this approach can be found in the International Commission on Radiological Protection Report 103 and the 2018 National Council on Radiation Protection and Measurements Commentary 27.

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Friday, September 14, 2018 8:34 AM
**To:** Konkus, John <konkus.john@epa.gov>

**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thank you.

Sent from my iPhone

On Sep 14, 2018, at 8:30 AM, Konkus, John <konkus.john@epa.gov> wrote:

> Ellen: We're working on something more robust for you. Should have it this morning.
>
> John
>
> Sent from my iPhone
>
> On Sep 14, 2018, at 5:52 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
>> Hi, Enesta,
>>
>> That EPA website entry you sent me a link to seems to be a contradictory statements saying exposures below 10 rem usually have no harmful health effects but the EPA still follows the guideline that no exposure is safe.
>>
>> When does that entry date from? When was it revised and what part was revised?
>>
>> Your other statement provides no information at all, except to indicate the EPA may decide to reverse its longstanding policy on radiation exposure without any advance notice to the public it is considering doing that.
>>
>> Can you answer my questions and provide an EPA expert to speak to? These are non-answers and public silence on important public health questions for Americans.
>>
>> Best,
>> Ellen
>>
>> Sent from my iPhone
>>
>> On Sep 13, 2018, at 6:01 PM, Jones, Enesta <Jones.Enesta@epa.gov> wrote:
>>
>>> Ellen,
>>> I inadvertently cut off the end of our response. Here it is:
>>>
>>> Find more information here: https://www.epa.gov/radiation/radiation-health-effects
>>>
>>> Ellen,
>>>
>>> "EPA is currently reviewing the more than 590,000 comments on the Strengthening Transparency in Regulatory Sciences proposal. The EPA will determine a timeline for a decision after it has more fully assessed the comments." — **EPA spokesperson**

On Sep 13, 2018, at 10:32 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:

Hello – wanted to also ask, is this still EPA policy?
https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
"Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."

"Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."

Best,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>
**Cc:** 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From**: Edwards, Jonathan [Edwards.Jonathan@epa.gov]
**Sent**: 9/14/2018 3:21:01 PM
**To**: Konkus, John [konkus.john@epa.gov]
**CC**: Jones, Enesta [Jones.Enesta@epa.gov]; Veal, Lee [Veal.Lee@epa.gov]; Griggs, John [Griggs.John@epa.gov]
**Subject**: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

[Removed reporter's email address]

# Ex. 5 Deliberative Process (DP)

Jon Edwards
Director
Office of Radiation and Indoor Air
202.343.9437

---

**From:** Konkus, John
**Sent:** Friday, September 14, 2018 10:53 AM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

The Radiation Health Effects site reflects recent information and was last updated in July 2018.

EPA's proposed rule on Strengthening Transparency in Regulatory Science did not discuss radiation. The Agency did seek comment on increasing transparency of the assumptions underlying dose response models. As noted previously, the timeline for any future action on this proposal has not yet been determined and EPA is reviewing more than 500,000 comments.

EPA continues to use the linear-no-threshold model for population-level radiation protection purposes. The EPA's Radiation Protection Program acknowledges uncertainty regarding health effects at low doses and is supportive of continued research in this area. More information in support of this approach can be found in the International Commission on Radiological Protection Report 103 and the 2018 National Council on Radiation Protection and Measurements Commentary 27.

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Friday, September 14, 2018 8:34 AM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thank you.

Sent from my iPhone

On Sep 14, 2018, at 8:30 AM, Konkus, John <konkus.john@epa.gov> wrote:

> Ellen: We're working on something more robust for you. Should have it this morning.
>
> John
>
> Sent from my iPhone
>
> On Sep 14, 2018, at 5:52 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
>> Hi, Enesta,
>>
>> That EPA website entry you sent me a link to seems to be a contradictory statements saying exposures below 10 rem usually have no harmful health effects but the EPA still follows the guideline that no exposure is safe.
>>
>> When does that entry date from? When was it revised and what part was revised?
>>
>> Your other statement provides no information at all, except to indicate the EPA may decide to reverse its longstanding policy on radiation exposure without any advance notice to the public it is considering doing that.
>>
>> Can you answer my questions and provide an EPA expert to speak to? These are non-answers and public silence on important public health questions for Americans.
>>
>> Best,
>> Ellen
>>
>> Sent from my iPhone
>>
>> On Sep 13, 2018, at 6:01 PM, Jones, Enesta <Jones.Enesta@epa.gov> wrote:
>>
>>> Ellen,
>>> I inadvertently cut off the end of our response. Here it is:
>>>
>>> Find more information here: https://www.epa.gov/radiation/radiation-health-effects
>>>
>>> Ellen,
>>>
>>> "EPA is currently reviewing the more than 590,000 comments on the Strengthening Transparency in Regulatory Sciences proposal. The EPA will determine a timeline for a decision after it has more fully assessed the comments." — **EPA spokesperson**
>>>
>>> On Sep 13, 2018, at 10:32 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>>>
>>> Hello – wanted to also ask, is this still EPA policy?

https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
"Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."

"Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."

Best,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>
**Cc:** 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to

me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From**: Veal, Lee [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=EB5E1FDE4D7041539934F58976A20FC2-VEAL, LEE]
**Sent**: 2/19/2019 5:17:28 PM
**To**: Edwards, Jonathan [Edwards.Jonathan@epa.gov]; Griggs, John [Griggs.John@epa.gov]; Jessica Wieder [Wieder.Jessica@epa.gov]
**Subject**: FW: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

https://www.latimes.com/local/california/la-me-secret-science-20190219-story.html

FYI -

Lee Ann B. Veal
Director, Radiation Protection Division
Office of Radiation and Indoor Air
Office: 202-343-9448; Cell: Ex. 6 Personal Privacy (PP)
www.epa.gov/radiation

---

**From:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Sent:** Tuesday, February 19, 2019 11:02 AM
**To:** Konkus, John <konkus.john@epa.gov>; Feldman, Carole <CFeldman@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>; Block, Molly <block.molly@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, John. I saw the LA Times story today saying Calabrese wrote that portion of the EPA rule.

So the answer to my question here last October was a yes, correct?

And when you all said you don't know why the EPA's press release quoted Calabrese on the rule – that was false, right?

Thanks,
Ellen

---

**From:** Knickmeyer, Ellen
**Sent:** Monday, October 01, 2018 1:33 PM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, John,
On the part of the Transparency rule that deals with dose-response for radiation and chemicals, and says regulators should consider alternate theories in addition to LNT, did Edward Calabrese and or Steven Milloy play a role in crafting it?
Best,

Ellen

**From:** Konkus, John <konkus.john@epa.gov>
**Sent:** Friday, September 14, 2018 10:53 AM
**To:** Knickmeyer, Ellen <EKnickmeyer@ap.org>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

The Radiation Health Effects site reflects recent information and was last updated in July 2018.

EPA's proposed rule on Strengthening Transparency in Regulatory Science did not discuss radiation. The Agency did seek comment on increasing transparency of the assumptions underlying dose response models. As noted previously, the timeline for any future action on this proposal has not yet been determined and EPA is reviewing more than 500,000 comments.

EPA continues to use the linear-no-threshold model for population-level radiation protection purposes. The EPA's Radiation Protection Program acknowledges uncertainty regarding health effects at low doses and is supportive of continued research in this area. More information in support of this approach can be found in the International Commission on Radiological Protection Report 103 and the 2018 National Council on Radiation Protection and Measurements Commentary 27.

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Friday, September 14, 2018 8:34 AM
**To:** Konkus, John <konkus.john@epa.gov>
**Cc:** Jones, Enesta <Jones.Enesta@epa.gov>; Press <Press@epa.gov>; Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** Re: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Thank you.

Sent from my iPhone

On Sep 14, 2018, at 8:30 AM, Konkus, John <konkus.john@epa.gov> wrote:

> Ellen: We're working on something more robust for you. Should have it this morning.
>
> John
>
> Sent from my iPhone
>
> On Sep 14, 2018, at 5:52 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
> > Hi, Enesta,
> >
> > That EPA website entry you sent me a link to seems to be a contradictory statements saying exposures below 10 rem usually have no harmful health effects but the EPA still follows the guideline that no exposure is safe.
> >
> > When does that entry date from? When was it revised and what part was revised?

Your other statement provides no information at all, except to indicate the EPA may decide to reverse its longstanding policy on radiation exposure without any advance notice to the public it is considering doing that.

Can you answer my questions and provide an EPA expert to speak to? These are non-answers and public silence on important public health questions for Americans.

Best,
Ellen

Sent from my iPhone

On Sep 13, 2018, at 6:01 PM, Jones, Enesta <Jones.Enesta@epa.gov> wrote:

> Ellen,
> I inadvertently cut off the end of our response. Here it is:
>
> Find more information here: https://www.epa.gov/radiation/radiation-health-effects
>
> Ellen,
>
> "EPA is currently reviewing the more than 590,000 comments on the Strengthening Transparency in Regulatory Sciences proposal. The EPA will determine a timeline for a decision after it has more fully assessed the comments." — **EPA spokesperson**
>
> On Sep 13, 2018, at 10:32 AM, Knickmeyer, Ellen <EKnickmeyer@ap.org> wrote:
>
> Hello – wanted to also ask, is this still EPA policy?
> https://www.epa.gov/sites/production/files/2015-05/documents/low-dose-284-291.pdf
> "Radiation protection, like the regulation of other carcinogenic agents, is—in the absence of compelling evidence to the contrary—predicated on the linear, no-threshold (LNT) hypothesis, which assumes that the risk of cancer due to a low dose exposure is proportional to dose, with no threshold."
>
> "Given the current state of the science, the consensus positions of key scientific and governmental bodies, as well as the conservatism and calculational convenience of the LNT assumption, it is unlikely that EPA will modify this approach in the near future."
>
> Best,
> Ellen
>
> ---
>
> **From:** Knickmeyer, Ellen
> **Sent:** Thursday, September 13, 2018 10:06 AM
> **To:** 'press@epa.gov' <press@epa.gov>; 'Konkus, John' <konkus.john@epa.gov>

**Cc:** 'edwards.jonathan@epa.gov' <edwards.jonathan@epa.gov>; 'veal.lee@epa.gov' <veal.lee@epa.gov>; 'griggs.john@epa.gov' <griggs.john@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the

intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at +1-212-621-1500 and delete this email. Thank you.

Message

**From**: Veal, Lee [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=EB5E1FDE4D7041539934F58976A20FC2-VEAL, LEE]
**Sent**: 9/13/2018 4:36:03 PM
**To**: Wieder, Jessica [Wieder.Jessica@epa.gov]; DeCair, Sara [DeCair.Sara@epa.gov]; Boyd, Mike [Boyd.Mike@epa.gov]
**CC**: Holden, Patricia [Holden.Patricia@epa.gov]
**Subject**: RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

We probably don't need to meet now, I have Jess' draft.

Lee Ann B. Veal
Director, Radiation Protection Division
Office of Radiation and Indoor Air
Office: 202-343-9448; Cell: Ex. 6 Personal Privacy (PP)
www.epa.gov/radiation

---

**From:** Wieder, Jessica
**Sent:** Thursday, September 13, 2018 11:08 AM
**To:** DeCair, Sara <DeCair.Sara@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Boyd, Mike <Boyd.Mike@epa.gov>
**Cc:** Holden, Patricia <Holden.Patricia@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

I am working on a draft response. My schedule is crazy today, but I can move meetings. Nothing is set in stone.

Jessica Wieder
Director, Center for Radiation Information and Outreach
U.S. Environmental Protection Agency
Radiation Protection Program
w: 202-343-9201
c: Ex. 6 Personal Privacy (PP)

---

**From:** DeCair, Sara
**Sent:** Thursday, September 13, 2018 11:07 AM
**To:** Veal, Lee <Veal.Lee@epa.gov>; Wieder, Jessica <Wieder.Jessica@epa.gov>; Boyd, Mike <Boyd.Mike@epa.gov>
**Subject:** RE: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

I'll ask Patricia to find a time for us to talk. Thanks!

---

**From:** Veal, Lee
**Sent:** Thursday, September 13, 2018 10:08 AM
**To:** Wieder, Jessica <Wieder.Jessica@epa.gov>; Boyd, Mike <Boyd.Mike@epa.gov>; DeCair, Sara <DeCair.Sara@epa.gov>
**Subject:** FW: AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards
**Importance:** High

Lets chat today.

Lee Ann B. Veal
Director, Radiation Protection Division
Office of Radiation and Indoor Air
Office: 202-343-9448; Cell: Ex. 6 Personal Privacy (PP)
www.epa.gov/radiation

---

**From:** Knickmeyer, Ellen [mailto:EKnickmeyer@ap.org]
**Sent:** Thursday, September 13, 2018 10:06 AM
**To:** Press <Press@epa.gov>; Konkus, John <konkus.john@epa.gov>
**Cc:** Edwards, Jonathan <Edwards.Jonathan@epa.gov>; Veal, Lee <Veal.Lee@epa.gov>; Griggs, John <Griggs.John@epa.gov>
**Subject:** AP requesting interview with EPA radiation-protection officials regarding LNT standards vs. threshold, hormetic standards

Hi, all,
I'm doing a story on the current EPA expressing openness to moving away from the linear non-threshold standard for radiation protection and toward standards that maintain lower doses of radiation and other carcinogens can be of acceptably low risk or beneficial. That's as with Dr. Calabrese's comments in April on Mr. Pruitt's proposed science "transparency" rule, which the EPA cited in announcing the proposal:

**Dr. Edward J. Calabrese, Professor, Environmental Health Sciences, University of Massachusetts:** "The proposal represents a major scientific step forward by recognizing the widespread occurrence of non-linear dose responses in toxicology and epidemiology for chemicals and radiation and the need to incorporate such data in the risk assessment process

And as with last year's EPA guidance last year that emergency responders can safely tolerate "low doses" of radiation

https://www.epa.gov/sites/production/files/2017-07/documents/pags_comm_tool_p9.pdf

I need to finish the story by Tuesday afternoon. Can you please make an EPA radiation-protection or analytics senior official available to talk to me by Monday on the topic? Where has the EPA moved since April on the LNT vs. threshold vs. hormesis argument, have there been any more moves within EPA away from LNT, and what are EPA radiation officials' thoughts on the topic?

All best,
Ellen Knickmeyer
Ex. 6 Personal Privacy (PP)
eknickmeyer@ap.org
Ex. 6 Personal Privacy (PP)

The information contained in this communication is intended for the use of the designated recipients named above. If the reader of this communication is not the intended recipient, you are hereby notified that you have received this communication in error, and that any review, dissemination, distribution or copying of this communication is strictly prohibited. If you have received this communication in error, please notify The Associated Press immediately by telephone at 212-621-1500 and delete this email. Thank you.

Contact

**Full Name**: Edward Calabrese

**E-mail**: edwardc@schoolph.umass.edu

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 2/11/2019 1:06:38 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: new paper
**Attachments**: Environ Pollution-EPA Transparency.pdf

Dear Clint:

See the attached recently accepted paper on the EPA Transparency proposal as written by an international group of ecological toxicology oriented researchers.

Sincerely,

Ed Calalbrese

Environmental Pollution 246 (2019) 566–570

Contents lists available at ScienceDirect

Environmental Pollution

journal homepage: www.elsevier.com/locate/envpol

# Commentary: EPA's proposed expansion of dose-response analysis is a positive step towards improving its ecological risk assessment☆

Evgenios Agathokleous [a, b, *], Alessandro Anav [c], Valda Araminiene [d], Alessandra De Marco [e], Marisa Domingos [f], Mitsutoshi Kitao [a], Takayoshi Koike [b], William J. Manning [g], Elena Paoletti [c], Costas J. Saitanis [h], Pierre Sicard [i], Marcello Vitale [j], Wenjie Wang [k, l], Edward J. Calabrese [m]

[a] Hokkaido Research Center, Forestry and Forest Products Research Institute (FFPRI), Forest Research and Management Organization, 7 Hitsujigaoka, Sapporo, Hokkaido, 062-8516, Japan
[b] Research Faculty of Agriculture, Hokkaido University, Kita 9 Nishi 9, Sapporo, Hokkaido, 060-8589, Japan
[c] National Council of Research, Via Madonna del Piano 10, Sesto Fiorentino, Florence, 50019, Italy
[d] Institute of Forestry, Lithuanian Research Centre for Agriculture and Forestry, Girionys, 53101, Kaunas district, Lithuania
[e] Italian National Agency for New Technologies, Energy and the Environment (ENEA), C.R. Casaccia, S. Maria di Galeria, Rome, 00123, Italy
[f] Instituto de Botânica, Núcleo de Pesquisa em Ecologia, PO Box 68041, 04045-972, SP, Brazil
[g] Department of Plant, Soil and Insect Sciences, University of Massachusetts, Amherst, MA, USA
[h] Lab of Ecology and Environmental Science, Agricultural University of Athens, Iera Odos 75, Athens, 11855, Greece
[i] ARGANS, 260 route du Pin Montard, Sophia Antipolis cedex, 06904, France
[j] Department of Environmental Biology, Sapienza University of Rome, Piazzale Aldo Moro 5, Rome, 00185, Italy
[k] Northeast Institute of Geography and Agroecology, Chinese Academy of Sciences, Changchun, 130102, China
[l] Northeast Forestry University, Harbin, 150040, China
[m] Department of Environmental Health Sciences, Morrill I, N344, University of Massachusetts, Amherst, MA, 01003, USA

ARTICLE INFO

*Article history:*
Received 26 September 2018
Received in revised form
11 December 2018
Accepted 15 December 2018
Available online 18 December 2018

*Keywords:*
Dose-response
Hormesis
Non-linear response
Regulation
Risk assessment

ABSTRACT

The United States Environmental Protection Agency (US EPA) has recently proposed changes to strengthen the transparency of its pivotal regulatory science policy and procedures. In this context, the US EPA aims to enhance the transparency of dose-response data and models, proposing to consider for the first time non-linear biphasic dose-response models. While the proposed changes have the potential to lead to markedly improved ecological risk assessment compared to past and current approaches, we believe there remain open issues for improving the quality of ecological risk assessment, such as the consideration of adaptive, dynamic and interactive effects. Improved risk assessment including adaptive and dynamic non-linear models (beyond classic threshold models) can enhance the quality of regulatory decisions and the protection of ecological health. We suggest that other countries consider adopting a similar scientific-regulatory posture with respect to dose-response modeling via the inclusion of non-linear biphasic models, that incorporate the dynamic potential of biological systems to adapt (i.e., enhancing positive biological endpoints) or maladapt to low levels of stressor agents.

© 2018 Elsevier Ltd. All rights reserved.

## 1. Introduction

While the history of dose-response assessment can be traced back to the late 19th century, its application for risk assessment began in the early 20th century with the development of public drinking water (US Public Health Service, 1925) and occupational health standards for chemicals and ionizing radiation (Calabrese, 2009).

During the mid-decades of the 20th century, there was a substantial expansion of recommended occupational health standards at the state level, and by national/international advisory groups. In 1970, the US Occupational Health and Safety Administration adopted several hundred recommended health standards of the American Conference of Governmental Industrial Hygienists,

☆ This paper has been recommended for acceptance by Prof. Dr. Klaus Kümmerer.

* Corresponding author. Hokkaido Research Center, Forestry and Forest Products Research Institute (FFPRI), Forest Research and Management Organization, 7 Hitsujigaoka, Sapporo, Hokkaido, 062-8516, Japan.
*E-mail addresses:* evgenios@affrc.go.jp, globalscience@frontier.hokudai.ac.jp (E. Agathokleous).

https://doi.org/10.1016/j.envpol.2018.12.046
0269-7491/© 2018 Elsevier Ltd. All rights reserved.

essentially all following a threshold dose-response model. By the end of the 1970s, all regulatory agencies in the US had transitioned to two-tier approach: one, with threshold, for non-carcinogens, and another, linear no-threshold (LNT), for carcinogens (Calabrese, 2009, 2018a).

These regulatory actions initially assumed a threshold dose-response model. The threshold model was generally recognized and accepted over the first several decades of the 20th century. The threshold dose-response model concept would be first challenged following the report of Muller in 1927 that X-rays produced gene mutations in fruit flies (Muller, 1927). In 1930, Muller proposed the concept of a Proportionality Rule (i.e. linear dose-response) to characterize the effects of ionizing radiation on assumed gene mutation, based on transgenerational phenotypic changes in fruit flies (Muller, 1930). Over the next 25 years there was a growing tension, amongst some members of the radiation genetics and medical communities over whether the threshold dose-response model should be replaced by a linear one for radiation (and later chemicals) inducing gene mutation (Calabrese, 2016, 2018b). After numerous disputes, a major change occurred in 1956 when the US National Academy of Sciences Biological Effects of Atomic Radiation (BEAR-1) Genetics Panel declared in an influential and well-publicized report that there was no threshold for assumed gene mutations in reproductive cells (Calabrese, 2017a, 2017b, 2018a). The idea promoted by BEAR-1 Genetics Panel was generalized to somatic cells and applied to cancer risk assessment, within several years (Calabrese, 2014). These changes led to a two tier system for risk assessment, one for carcinogens following a linear model and one for non-carcinogens following a threshold model. The linear model assumed that induced gene mutations were not repairable and the damage was cumulative, leading to the belief that total dose, rather than dose rate, was the best predictor of gene mutation. The LNT model was adopted by the US Environmental Protection Agency (EPA) for carcinogen risk assessment for ionizing radiation and chemical carcinogen in the mid- 1970s, and continues to the present.

With respect to ecological risk assessment (ERA) (Supplementary Materials, Fig. 1S), the issue was not recognized as significant as in the case of cancer and human toxicology. As a result of this differential viewing of human versus ecological effects, the general course of action for ERA was framed by the assumption of the threshold dose-response model, during the later decades of the 20th century (Calabrese and Baldwin, 1993). However, over this time period new perspectives and challenges emerged that could affect the process of carcinogen and non-carcinogen risk assessment for humans, and for ecological receptors. A potential significant development involved the rediscovery and substantial documentation of the hormetic-biphasic dose-response that may be applied to human health and to ERA for chemicals and radiation (Calabrese, 2001, Calabrese and Baldwin, 2000a,b, 2001; Vom Saal, 2007; Calabrese 2008, 2011; see www.BELLEonline.com (newsletters) for a substantial number of scholarly articles on this topic both supporting and challenging the approaches of hormesis in risk assessment). A second significant development was the concept that linear dose responses (Calabrese, 2017a, 2018a) may be applied to non-cancer endpoints (Bogen, 2016, 2017) such as lead-induced neurotoxicity (USEPA, 1998), particulate matter effects on humans (WHO, 2006; USEPA, 2013; Enstrom, 2017), effects of endocrine disruptor agents on humans (Zoeller et al., 2015; Schug et al., 2016), and ozone-induced plant injury (Agathokleous et al., 2019a).

To date, major regulatory agencies have adopted the LNT dose-response model for the particulate matter effects on humans (WHO, 2006; USEPA, 2013), and for the ozone effects on plants to derive critical levels for vegetation protection (Agathokleous et al., 2019a). The adoption of the LNT for these two particular agents is significant by itself, but also important because it can trigger such adoptions by other regulatory changes concerning other agents and endpoints.

## 2. Analysis

The nature of the dose-response relationship is a critical factor guiding the risk assessment and eventually driving the estimates of potential risk. While risk assessment has long been based upon linear or threshold dose-response relationships, it is now recognized that linear and threshold dose-response relationships are often not the norm and that the dose-response relationship can be non-linear polyphasic (Costantini et al., 2010; Calabrese, 2017c; Calabrese and Mattson, 2017; Agathokleous et al., 2018a, 2019a,b; Kim et al., 2018; Leak et al., 2018) (note: for the debate on hormesis, the reader may also refer e.g. to Kefford et al., 2008; Ricci and Sammis, 2012; Sacks and Siegel, 2016, 2017; Mushak, 2013a,b; Jargin, 2018; www.BELLEonline.com - see newsletters). In light of the significance of these advances in regulatory science, the EPA has recently proposed changes to strengthen the transparency of its regulatory science[1] (USEPA, 2018). Of relevance to the present paper is that the EPA proposes moving away from the use of linearity as a default model for risk assessment, providing for the first time an opportunity to consider non-linear functions beyond the threshold model.[2]

Current scientific findings indicate that non-linear dose response modeling is more biologically plausible than low dose linear modeling (Costantini et al., 2010; Calabrese and Mattson, 2017; Agathokleous et al., 2018a, 2019a; Kim et al., 2018; Leak et al., 2018). Hence, we believe that consideration of alternative models has the potential to enhance the quality of both risk estimates and subsequent risk management decisions that guide the derivation of environmental standards and cost-benefit assessments.

In the last two decades it was extensively shown that biphasic (e.g. *U*-shaped, *J*-shaped, and bell-shaped) dose responses are induced by a variety of chemical agents and environmental factors in a wide spectrum of endpoints and biological models, not only at individual but also at community level, including key ecological endpoints such as biodiversity, soil respiration, emission of leaf volatile organic compounds (VOCs), gas fluxes from soils, demography of pests of agricultural crops, and reproduction of terrestrial and aquatic organisms (Costantini et al., 2010; Schreck, 2010; Calabrese and Blain, 2011; Calabrese and Mattson, 2017; Agathokleous, 2018; Agathokleous et al., 2018a,b, 2019a; Kim et al., 2018; Leak et al., 2018; Sial et al., 2018; Yue et al., 2018). We thus believe consideration of non-linear models has the potential to significantly improve risk estimation.[3]

[1] The first part of the EPA proposal excludes scientific studies whose data are not publicly accessible. Many scientific societies have not supported the EPA proposal, and thousands of comments have been submitted criticizing the study exclusion part (EPA, Docket ID: EPA-HQ-OA-2018-0259, https://www.regulations.gov/docket?D=EPA-HQ-OA-2018-0259). This paper is not intended to appraise the study exclusion part of the EPA proposal.

[2] EPA mentions "EPA should also incorporate the concept of model uncertainty when needed as a default to optimize low dose risk estimation based on major competing models, including linear, threshold, and U-shaped, J-shaped, and bell-shaped models" (USEPA, 2018). While it is unclear what "when needed" is supposed to mean, we suggest that "when needed" is when the data are inadequate for confident modeling as in the case of substantial extrapolation beyond the observable data. For argumentation purposes, this would include extrapolation approximately two-fold beyond the observable data.

[3] For an alternative view on contested subjects, the reader may refer to the comments by Finkel (2018) on the EPA website.

The EPA states it should give "appropriate consideration"[4] to high quality studies that explore: i) "a broad class of parametric concentration-response models with a robust set of potential confounding variables"; ii) "nonparametric models that incorporate fewer assumptions"; iii) "various threshold models across the exposure range"; and iv) "spatial heterogeneity" (USEPA, 2018).

We consider this proposal an important step towards a more dynamic and flexible risk assessment process which will not view animals, plants, and ecosystems as static but as dynamic biological entities displaying complex responses to different environmental conditions. For instance, the need for dynamic risk assessment is highlighted for vegetation response to gases which is driven by soil water and nutrient availability (Körner, 2006; Proietti et al., 2016; Anav et al., 2018) as well as by meteorological seasonality, as it occurs in subtropical regions exposed to well defined wet and dry periods (Moura et al., 2014). In addition, two aspects may be considered in subtropical regions: i) pioneer tree species from forest plots may be more acclimated to the stressful environment than non-pioneer trees, presenting better conditions to perpetuate in the disturbed forest remnants; and ii) multilinear regression analyses revealed that the oscillations in the physiological leaf traits in both functional groups of tree species coincide with oscillations in both meteorological variables and air pollutants, notably air temperature, global solar radiation, ozone and nitrogen dioxide (Esposito et al., 2018). Interaction between variables (De Marco et al., 2014; Vitale et al., 2014) is an important reason for considering more complex dose-response functions and dynamic risk assessment.

With regard to proposition iii of the EPA, we believe that biological plausibility linked with appropriate experimental studies of high quality should guide low dose modeling strategies. This approach can enhance the likelihood of improved biodiversity risk estimates (Pereira et al., 2010). We therefore believe the EPA proposal is a positive step towards scientifically-based biologically motivated ERA. However, while this is a significant advance, we believe there remain open issues that need to be addressed in order to improve ERA:

- **Integration of adaptive response in ERA modeling:** Adaptive responses are a fundamental feature of evolution and these processes are often described by hormetic dose responses with specific quantitative features that are highly generalizable across aquatic and terrestrial organisms (Laughlin et al., 1981; Cedergreen et al., 2007; Costantini et al., 2010; Schreck, 2010; Calabrese and Blain, 2011; Hook et al., 2014; Ng et al., 2016; Calabrese and Mattson, 2017; Iavicoli et al., 2018; Agathokleous, 2018; Agathokleous et al., 2018a, 2019a,b; Oliveira et al., 2018; Leak et al., 2018). These findings support the use of hormesis and other non-linear dose-response models in terrestrial and aquatic ERA.
- **Integration of space/time variables in ERA modeling:** With respect to biphasic dose-response relationships, both space and time should be considered. Low-dose effects often show temporal fluctuations, with declining stimulatory responses over time (Agathokleous et al., 2019b; Leak et al., 2018; Sun et al., 2018).
- **Life histories of species role in ERA:** Low dose effects may be influenced by the life histories of species or ecotypes (McCallum et al., 2019). The developmental/ontogenic stage for which the dose-response is studied should be considered. For instance, this would mean that a potential net benefit should be considered at the long term, possibly after exposure throughout the biological cycle, or over several growing seasons for perennial plants. Therefore, a future target would be to incorporate the life history of the communities/populations for which the low-dose risk is estimated.
- **The endpoint matters:** Ecological systems are complex and a single endpoint may fail to reflect the most relevant outcome in ecological terms (Hook et al., 2014; Agathokleous et al., 2019a,c). By integrating multiple relevant endpoints, the capacity for classifying the low-dose effect as positive (beneficial) or negative (potentially harmful in the long run) may be enhanced (Hook et al., 2014; Agathokleous et al., 2019c).
- **Transgenerational ERA:** The present is not likely to mirror the future. Recent advances have revealed that effects of low doses on animals can affect the next generations via epigenetic mechanisms (Emborski and Mikheyev, 2018; Kishimoto et al., 2018; Mothersill and Seymour, 2018). This transgenerational preconditioning mode may lead to offspring with altered tolerance (increase or decrease) to stress. Therefore, risk estimates of one generation may not necessarily reflect risk estimates of next generations.
- **Interindividual variation:** The current ERA is based on experiments with controlled conditions and commonly where the subject organisms are at a healthy biological state. This raises important considerations whether the dose-response outcomes can be translated to real-world conditions. In fact, recent epidemiological studies have shown little or no evidence of ozone-induced injury in perennial vegetation (Agathokleous et al., 2019a). Furthermore, extensive research indicates that plant response to gases differs between open systems, where plants fully interact with the environment, and semi-closed systems, where the infrastructure creates and maintains a microenvironment different from the ambient conditions (Valkama et al., 2007; Feng et al., 2018). Notably, data from semi-closed systems comprised the base for present ERA. These examples suggest that environmental risk assessment can be improved with real-world or near real-world study conditions (Sicard et al., 2016).
- **Community level data needed in ERA:** Dose-response experiments at community level are scarce. The current risk assessment is principally based upon experiments where the response of individual organisms is studied. However, individual organisms may respond differently when coexisting with other individuals, so called forming populations (González-Fernández et al., 2017). A future target of risk assessment would be the implementation of dose responses where organisms are under the influence of competition with coexisting organisms, as typically happens in the nature.
- **Mixture toxicity and ERA:** Dose response modeling needs to address the issue of complex chemical mixtures (Belz et al., 2008; Ge et al., 2011; Zou et al., 2013; Mayo et al., 2015; Belz and Piepho, 2017; Docea et al., 2018; Liu et al., 2018).

## 3. Conclusions

This paper strongly supports the EPA proposal to move away from the use of LNT as a default in risk assessment and to consider non-linear models such as hormesis. It is scientifically necessary for EPA to incorporate evolutionarily based biologically motivated models for ecosystem risk assessment. Other countries should consider following this part of EPA's proposal.

## Conflicts of interest

The authors declare no conflict of interest.

[4] It has not been properly defined by the EPA what "appropriate consideration" is supposed to mean. We consider "high quality studies" studies with robust experimental design, documented quality control, and with correct statistical testing and inference, with raw data being publicly available or not (see footnote 1).

## Funding

E.A. is an International Research Fellow (ID No: P17102) of the Japan Society for the Promotion of Science. JSPS is a non-profit, independent administrative institution. WW acknowledges fund support from China's National Foundation of Natural Sciences (41730641, 31670699) and the Fundamental Research Funds for the Central Universities (2572017DG04, 2572017EA03). EJC acknowledges longtime support from the U.S. Air Force (AFOSR FA9550-13-1-0047) and ExxonMobil Foundation (S18200000000256). The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to and where to submit for publication consideration.

## Acknowledgments

This paper was prepared within the International Union of Forest Research Organizations (IUFRO) Task Force on "Climate Change and Forest Health" and IUFRO WP7.01.09 "Ground–level ozone" and WP7.01.05 "Modelling and risk assessment". E.J.C was asked by EPA to informally review the EPA transparency draft proposal. He provided comments on the dose response feature of the proposal. He was not paid or otherwise compensated for this effort. EJC was also invited by the US Senate to offer testimony on the EPA proposal. This testimony was provided on October 3, 2018 in Washington DC. The testimony of EJC is now in press at Journal of Cell Communication and Signaling (Calabrese, 2018c).

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envpol.2018.12.046.

## References

Agathokleous, E., 2018. Environmental hormesis, a fundamental non-monotonic biological phenomenon with implications in ecotoxicology and environmental safety. Ecotoxicol. Environ. Saf. 148, 1042–1053.
Agathokleous, E., Kitao, M., Calabrese, E.J., 2018a. Human and veterinary pharmaceuticals induce hormesis in plants: scientific and regulatory issues and an environmental perspective. Environ. Int. 120, 489–495.
Agathokleous, E., Kitao, M., Calabrese, E.J., 2018b. Emission of volatile organic compounds from plants shows a biphasic pattern within an hormetic context. Environ. Pollut. 239, 316–321.
Agathokleous, E., Belz, R.G., Calatayud, V., et al., 2019a. Predicting the effect of ozone on vegetation via linear non-threshold (LNT), threshold and hormetic dose-response models. Sci. Total Environ. 649, 61–74.
Agathokleous, E., Kitao, M., Calabrese, E.J., 2019b. Hormetic dose responses induced by lanthanum in plants. Environ. Pollut. 244, 332–341.
Agathokleous, E., Belz, R.G., Kitao, M., Koike, T., Calabrese, E.J., 2019c. Does the root to shoot ratio show a hormetic response to stress? An ecological and environmental perspective. J. For. Res. 30 https://doi.org/10.1007/s11676-018-0863-7.
Anav, A., Proietti, C., Menut, L., Carnicelli, S., De Marco, A., Paoletti, E., 2018. Sensitivity of stomatal conductance to soil moisture: implications for tropospheric ozone. Atmos. Chem. Phys. 18, 5747–5763.
Belz, R.G., Piepho, H.P., 2017. Predicting biphasic responses in binary mixtures: pelargonic acid versus glyphosate. Chemosphere 178, 88–98.
Belz, R.G., Cedergreen, N., Sørensen, H., 2008. Hormesis in mixtures — can it be predicted? Sci. Total Environ. 404, 77–87.
Bogen, K.T., 2016. Linear-no-threshold default assumptions for noncancer and nongenotoxic cancer risks: a mathematical and biological critique. Risk Anal. 36, 589–604.
Bogen, K.T., 2017. Linear-no-threshold default assumptions are unwarranted for cytotoxic endpoints independently triggered by ultrasensitive molecular switches. Risk Anal. 37, 1808–1816.
Calabrese, E.J., 2001. The frequency of U-shaped dose responses in the toxicological literature. Toxicol. Sci. 62, 330–338.
Calabrese, E.J., 2008. Hormesis: why it is important to toxicology and toxicologists. Environ. Toxicol. Chem. 27, 1451–1474.
Calabrese, E.J., 2009. The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment. Arch. Toxicol. 83, 203–225.
Calabrese, E.J., 2011. Toxicology rewrites its history and rethinks its future: giving equal focus to both harmful and beneficial effects. Environ. Toxicol. Chem. 30, 2658–2673.
Calabrese, E.J., 2014. The Genetics Panel of the NAS BEAR I Committee (1956): epistolary evidence suggests self-interest may have prompted an exaggeration of radiation risks that led to the adoption of the LNT cancer risk assessment model. Arch. Toxicol. 88, 1631–1634.
Calabrese, E.J., 2016. LNTgate: how scientific misconduct by the U.S. NAS led to governments adopting LNT for cancer risk assessment. Environ. Res. 148, 535–546.
Calabrese, E.J., 2017a. The threshold vs LNT showdown: dose rate findings exposed flaws in the LNT model part 1. The Russell-Muller debate. Environ. Res. 154, 435–451.
Calabrese, E.J., 2017b. Flaws in the LNT single-hit model for cancer risk: an historical assessment. Environ. Res. 158, 773–788.
Calabrese, E.J., 2017c. Hormesis commonly observed in the assessment of aneuploidy in yeast. Environ. Pollut. 225, 713–728.
Calabrese, E.J., 2018a. The additive to background assumption in cancer risk assessment: a reappraisal. Environ. Res. 166, 175–204.
Calabrese, E.J., 2018b. From Muller to mechanism: how LNT became the default model for cancer risk assessment. Environ. Pol. 241, 289–302.
Calabrese, E.J., 2018c. EPA transparency proposal: testimony of Edward J. Calabrese, Ph.D, October 3, 2018. J. Cell Comm. Sign. https://doi.org/10.1007/s12079-018-0497-8.
Calabrese, E.J., Baldwin, L.A., 1993. Performing Ecological Risk Assessments. Lewis Publishers, Chelsea, p. 288.
Calabrese, E.J., Baldwin, L.A., 2000a. Radiation hormesis: its historical foundations as a biological hypothesis. Hum. Exp. Toxicol. 19, 41–75.
Calabrese, E.J., Baldwin, L.A., 2000b. Chemical hormesis: its historical foundations as a biological hypothesis. Hum. Exp. Toxicol. 19, 2–31.
Calabrese, E.J., Baldwin, L.A., 2001. U-shaped dose-responses in biology, toxicology, and public health. Annu. Rev. Public Health 22, 15–33.
Calabrese, E.J., Blain, R.B., 2011. The hormesis database: the occurrence of hormetic dose responses in the toxicological literature. Regul. Toxicol. Pharmacol. 61, 73–81.
Calabrese, E.J., Mattson, M.P., 2017. How does hormesis impact biology, toxicology, and medicine? npj Aging Mech. Dis. 3, 13.
Cedergreen, N., Streibig, J.C., Kudsk, P., Mathiassen, S.K., Duke, S.O., 2007. The occurrence of hormesis in plants and algae. Dose-Response 5, 150–162.
Costantini, D., Metcalfe, N.B., Monaghan, P., 2010. Ecological processes in a hormetic framework. Ecol. Lett. 13, 1435–1447.
De Marco, A., Proietti, C., Cionni, I., Fischer, R., Screpanti, A., Vitale, M., 2014. Future impacts of nitrogen deposition and climate change scenarios on forest crown defoliation. Environ. Pollut. 194, 171–180.
Docea, A.O., Gofita, E., Goumenou, M., Calina, D., Rogoveanu, O., Varut, M., Olaru, C., Kerasioti, E., Fountoucidou, P., Taitzoglou, I., Zlatian, O., Rakitskii, V.N., Hernandez, A.F., Kouretas, D., Tsatsakis, A., 2018. Six months exposure to a real life mixture of 13 chemicals' below individual NOAELs induced non monotonic sex-dependent biochemical and redox status changes in rats. Food Chem. Toxicol. 115, 470–481.
Eroborski, C., Mikheyev, A., 2018. Ancestral Diet Leads to Dynamic Transgenerational Plasticity for Five Generations in *Drosophila melanogaster*. bioRxiv, p. 273144.
Enstrom, J.E., 2017. Fine particulate matter and total mortality in cancer prevention study cohort reanalysis. Dose-response 15, 1559325817693345.
Esposito, M.P., Nakazato, R.K., Pedroso, A.N.V., Lima, M.E.L., Figueiredo, M.A., Diniz, A.P., Kozovits, A.R., Domingos, M., 2018. Oxidant-antioxidant balance and tolerance against oxidative stress in pioneer and non-pioneer tree species from the remaining Atlantic Forest. Sci. Total Environ. 625, 382–393.
Feng, Z., Uddling, J., Tang, H., Zhu, J., Kobayashi, K., 2018. Comparison of crop yield sensitivity to ozone between open-top chamber and free-air experiments. Global Change Biol. 24, 2231–2238.
Finkel, A.M., 2018. Comments on EPA "secret science" proposal. Comment on the environmental protection agency (EPA) proposed Rule: strengthening transparency in regulatory science, 30 August 2018. ID: EPA-HQ-OA-2018-0259-8771. https://www.regulations.gov/document?D=EPA-HQ-OA-2018-0259-8771.
Ge, H.-L., Liu, S.-S., Zhu, X.-W., Liu, H.-L., Wang, L.-J., 2011. Predicting hormetic effects of ionic liquid mixtures on luciferase activity using the concentration addition model. Environ. Sci. Technol. 45, 1623–1629.
Gonzalez-Fernández, I., Sanz, J., Calvete-Sogo, H., Elvira, S., Alonso, R., Bermejo-Bermejo, V., 2017. Validation of ozone response functions for annual Mediterranean pasture species using close-to-field-conditions experiments. Environ. Sci. Pollut. Res. 24, 26259–26268.
Hook, S.E., Gallagher, E.P., Batley, G.E., 2014. The role of biomarkers in the assessment of aquatic ecosystem health. Integrated Environ. Assess. Manag. 10, 327–341.
Iavicoli, I., Leso, V., Fontana, L., Calabrese, E.J., 2018. Nanoparticle exposure and hormetic dose–responses: an update. Int. J. Mol. Sci. 19, 805.
Jargin, S.V., 2018. Hormesis and radiation safety norms: comments for an update. Hum. Exp. Toxicol. 37, 1233–1243.

Kefford, B.J., Zalizniak, L., Warne, M.St.J., Nugegoda, D., 2008. Is the integration of hormesis and essentiality into ecotoxicology now opening Pandora's Box? Environ. Pollut. 151, 516–523.
Kim, S.-A., Lee, Y.-M., Choi, J.-Y., Jacobs, D.R., Lee, D.-H., 2018. Evolutionarily adapted hormesis-inducing stressors can be a practical solution to mitigate harmful effects of chronic exposure to low dose chemical mixtures. Environ. Pollut. 233, 725–734.
Kishimoto, S., Uno, M., Okabe, E., Nono, M., Nishida, E., 2018. Environmental stresses induce transgenerationally inheritable survival advantages via germline-tosoma communication in *Caenorhabditis elegans*. Nat. Commun. 8, 14031.
Körner, C., 2006. Plant $CO_2$ responses: an issue of definition, time and resource supply. New Phytol. 172, 393–411.
Laughlin Jr., R.B., Ng, J., Guard, H.E., 1981. Hormesis: a response to low environmental concentrations of petroleum hydrocarbons. Science 211, 705–707.
Leak, R.K., Calabrese, E.J., Kozumbo, W.J., et al., 2018. Enhancing and extending biological performance and resilience. Dose-Response 16, 1559325818878450.
Lu, Y., Guo, R., Tang, S., Zhu, F., Zhang, S., Yan, Z., Chen, J., 2018. Single and mixture toxicities of BDE-47, 6-OH-BDE-47 and 6-MeOBDE-47 on the feeding activity of *Daphnia magna*: from behavior assessment to neurotoxicity. Chemosphere 195, 542–550.
Mayo, M., Collier, Z.A., Winton, C., Chappell, M.A., 2015. Data-driven method to estimate nonlinear chemical equivalence. PLoS One 10, e0130494.
McCallum, M.L., Mary, M., Trauth, S.E., 2019. Life history trade-offs and the role of ectothermy in hormesis. BioRxiv. https://doi.org/10.1101/337279.
Mothersill, C., Seymour, C., 2018. Old data—new concepts: integrating "indirect effects" into radiation protection. Health Phys. 115, 170–178.
Moura, B.B., Alves, E.S., de Souza, S.R., Domingos, M., Vollenweider, P., 2014. Ozone phytotoxic potential with regard to fragments of the Atlantic semi-deciduous forest downwind of sao paulo, Brazil. Environ. Pollut. 192, 65–73.
Muller, H.-G., 1927. Artificial transformation of the gene. Science 66, 192–195.
Muller, H.-G., 1930. Radiation and genetics. Am. Nat. 64, 220–251.
Mushak, P., 2013a. How prevalent is chemical hormesis in the natural and experimental worlds? Sci. Total Environ. 443, 573–581.
Mushak, P., 2013b. Limits to chemical hormesis as a dose–response model in health risk assessment. Sci. Total Environ. 443, 643–649.
Ng, C.Y.P., Cheng, S.H., Yu, K.N., 2016. Hormetic effect induced by depleted uranium in zebrafish embryos. Aquat. Toxicol. (N. Y.) 175, 184–191.
Oliveira, M.F., Geilis, M.A., França, T.F.A., Moreira, D.C., Hermes-Lima, M., 2018. Is "preparation for oxidative stress" a case of physiological conditioning hormesis? Front. Physiol. 9, 645.
Pereira, H.M., Leadley, P.W., Proença, V., et al., 2010. Scenarios for global biodiversity in the 21st century. Science 330, 1496–1501.
Proietti, C., Anav, A., De Marco, A., Sicard, P., Vitale, M.A., 2016. A multi-sites analysis on the ozone effects on Gross Primary Production of European forests. Sci. Total Environ. 556, 1–11.
Ricci, P.F., Sammis, I.R., 2012. Regulatory-science: biphasic cancer models or the LNT—not just a matter of biology! Dose-Response 10, 120–154.
Sacks, B., Siegel, J.A., 2016. Jan Beyea mischaracterizes the work by Siegel et al. (2016). Environ. Res. 150, 663.
Sacks, B., Siegel, J.A., 2017. Preserving the anti-scientific linear no-threshold myth: authority, agnosticism, transparency, and the standard of care. Dose-Response 15, 1559325817717839.
Schreck, C.B., 2010. Stress and fish reproduction: the roles of allostasis and hormesis. Gen. Comp. Endocrinol. 165, 549–556.
Schug, T.T., Johnson, A.F., Birnbaum, L.S., et al., 2016. Minireview: endocrine disruptors: past lessons and future directions. Mol. Endocrinol. 30, 833–847.
Sial, M.U., Zhao, Z., Zhang, L., Zhang, Y., Mao, L., Jiang, H., 2018. Evaluation of insecticides induced hormesis on the demographic parameters of *Myzus persicae* and expression changes of metabolic resistance detoxification genes. Sci. Rep. 8, 16601.
Sicard, P., De Marco, A., Dalstein-Richier, L., Tagliaferro, F., Renou, C., Paoletti, E., 2016. An epidemiological assessment of stomatal ozone flux-based critical levels for visible ozone injury in Southern European forests. Sci. Total Environ. 541, 729–741.
Sun, H., Calabrese, E.J., Zheng, M., Wang, D., Pan, Y., Lin, Z., Liu, Y., 2018. A swinging seesaw as a novel model mechanism for time-dependent hormesis under dose-dependent stimulatory and inhibitory effects: a case study on the toxicity of antibacterial chemicals to *Aliivibrio fischeri*. Chemosphere 205, 15–23.
US Public Health Service, 1925. The physical and chemical characteristics of acceptable water supplies. Publ. Health Rep. 40, 693.
USEPA, 1998. Guidelines for neurotoxicity risk assessment. Fed. Regist. 63, 26926–26954.
USEPA, 2013. National Ambient Air Quality Standards for Particulate Matter; Final Rule, vol. 78. Federal Register.
USEPA, 2018. Strengthening transparency in regulatory science. Fed. Regist. 83, 18768–18774.
Valkama, E., Koricheva, J., Oksanen, E., 2007. Effects of elevated $O_3$, alone and in combination with elevated $CO_2$, on tree leaf chemistry and insect herbivore performance: a meta-analysis. Global Change Biol. 13, 184–201.
Vitale, M., Proietti, C., Cionni, I., Fischer, R., De Marco, A., 2014. Random forests analysis: a useful tool for defining the relative importance of environmental conditions on crown defoliation. Water, Air, Soil Pollut. 225, 1992.
Vom Saal, F.S., 2007. Hormesis controversy. Environ. Sci. Technol. 41, 3.
WHO, 2006. WHO Air Quality Guidelines for Particulate Matter, Ozone, Nitrogen Dioxide and Sulfur Dioxide. Global Update 2005, Summary of Risk Assessment. World Health Organization, Geneva. WHO/SDE/PHE/OEH/06.02.
Yue, P., Cui, X., Gong, Y., Li, K., Goulding, K., Liu, X., 2018. Impact of elevated precipitation, nitrogen deposition and warming on soil respiration in a temperate desert. Biogeosciences 15, 2007–2019.
Zoeller, R.T., Vandenberg, L.N., Becher, G., Bjerregaard, P., Bornman, R., Brandt, I., 2015. Assessing dose–response relationships for endocrine disrupting chemicals (EDCs): a focus on non-monotonicity. Environ. Health 14, 42.
Zou, X., Lin, Z., Deng, Z., Yin, D., 2013. Novel approach to predicting hormetic effects of antibiotic mixtures on *Vibrio fischeri*. Chemosphere 90, 2070–2076.

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 3/24/2019 7:29:36 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: new paper
**Attachments**: regulation-LNT.pdf

Clint:

See the attached new paper.

Ed

HEALTH & MEDICINE

# The Troubled History of Cancer Risk Assessment

*The Linear-No-Threshold paradigm, which asserts there are no safe exposure levels, is the product of flawed and corrupted science.*

BY EDWARD J. CALABRESE

When crafting regulations on exposure to carcinogens and other dangers, policymakers often vow to "follow the science" on what is safe and what is unsafe. But what if that science is flawed or grounded in questionable judgments—or worse?

In 1956, a National Academy of Sciences (NAS) panel formally recommended to the U.S. Government that it change how it assesses risk from ionizing radiation. That sounds innocuous enough, but the Biological Effects of Atomic Radiation (BEAR) I Genetics Panel's proposed change was momentous: switching from a threshold model in which exposure is deemed safe if kept below a certain level, to a linear model in which no exposure is considered safe. This recommendation would ultimately be accepted by leading regulatory and advisory bodies in the United States and internationally, and extended to other prospective hazards like chemical carcinogens.

As the saying goes, "As the twig is bent, so grows the tree." All subsequent cancer risk assessments in the United States and throughout the world would inherit the risk assessment paradigm from the NAS BEAR I Genetics Panel. But was this change sound?

## X-RAY MUTATIONS

The NAS BEAR I Genetics Panel based its recommendation mainly on a strongly held belief that all radiation-induced mutation was unrepairable, irreversible, cumulative, and linear in the matter of dose response. However, the empirical evidence for this view was weak and equivocal. Yet the recommendation had considerable authority because the panel was deemed by opinion leaders, including the *New York Times*, as a virtual genetics "dream team" that included a Nobel laureate, a future laureate, and others of high achievement and prestige.

The origin of the Linear-No-Threshold (LNT) belief was borne in the judgment and passion of Hermann Muller, who was the first to claim that X-rays induced gene mutations. Muller had indeed made a momentous breakthrough in late 1926 when he found a way to produce quickly copious transgenerational phenotypic changes (e.g., alterations in size, color, or shape) in fruit flies, which he interpreted as being the result of gene mutation. This was something that no one else had done. Muller believed that he had discovered the long-sought mechanism of evolution, as he claimed that he had produced the "artificial transmutation of the gene." He even introduced the term "point mutation" (i.e., very small mutational gene change) into the geneticist's lexicon.

Muller rushed to publish his discovery after only the first of the three seminal experiments that would ultimately earn him a Nobel Prize. However, the first article, published in the journal *Science*, offered no data, instead presenting a discussion of his observations. Several months later and with considerable suspense, he unveiled the data at a large conference in Berlin, to great acclaim. (The relevance of all this will be explained below.) His star rose meteorically and he became the clarion of "the new genetics" that gained insight into evolution as well as medical concerns resulting from excessive use of X-rays.

Just when the initial commotion settled down, Muller made headlines a second time, in 1930, when he announced that the nature of the dose response for X-ray-induced mutation was linear, all the way down to a single ionization. That is, he claimed, there is no safe exposure. He thought this idea was basic, a universal concept, occurring in all life, including the plant, microbe, and animal domains, and called it the "Proportionality Law."

EDWARD J. CALABRESE is professor of toxicology at the University of Massachusetts, Amherst.

PHOTO BY HULTON DEUTSCH / GETTY IMAGES

## MOUSE EXPERIMENTS SUPPORTING LNT

Muller's gene mutation breakthrough and his formulation of its implications in the Proportionality Law would lead several highly prestigious geneticist and physicist colleagues to provide a mechanism (i.e., gene target theory) of the X-ray-induced gene mutation Proportionality Rule. A 1935 paper presented the "linear non-threshold – single hit model" and applied it to mutation; it would later be applied to cancer. The NAS BEAR Genetics Panel would use this model in its 1956 recommendation.

The model was reaffirmed 16 years later with the next NAS committee, then called the U.S. Biological Effects of Ionizing Radiation (BEIR) Genetics Subcommittee. However, instead of using data from Muller's fruit flies, this committee based the LNT model on the massive mouse model experiments of William Russell of the Oak Ridge National Laboratory. Russell used over 2 million mice in his studies, a size that will likely never be approached again. The findings and the linearity recommendation became the basis for the Environmental Protection Agency's adoption of the LNT model and its regulatory applications to radiation and chemicals. This reflected the belief that cancer was mediated by a commonly shared mutation mechanism.

The BEIR recommendation has been the "gold standard" for exposure regulation, providing the assurance that linearity was "real" because of the limitations of epidemiological studies to confidently resolve dose-response relationships in the low-dose zone. In many ways, the Russell findings became the toxicology and risk assessment version of the Rosetta Stone. They offered a reliable translation of experimental and epidemiological studies to the language of human risk assessment.

## MULLER'S MISTAKE

The above summary is the "official" history of cancer risk assessment offered in most toxicology texts. However, several historical revelations have emerged over the past few years that have turned this entire story upside down. Those revelations affect the reputations of some very prestigious scientists, the validity of a Nobel Prize, and the scientific foundations of cancer risk assessment worldwide.

The problems with the "authoritative" cancer risk assessment story start with its foundation. Muller's claim to have induced gene *mutation* has been found to

Hermann Muller preparing one of his genetic experiments exposing fruit flies to X-rays.

be incorrect. He actually induced massive gene *deletions*, affecting chromosome (rather than a gene change) transgenerational phenotypic changes. This criticism of his work was raised while Muller was still alive, but he was able to stifle it. However, modern DNA/nucleotide analysis studies have shown the relevance of this criticism.

Muller's mistakes on the gene mutation interpretation invalidated the 1935 LNT–single hit model that was based on the assumption of gene mutation. Muller mistook an observation (i.e., transgenerational phenotypic changes) for a mechanism (gene mutation), conflating the two. He made a big mistake and perpetuated it for decades, with profound consequences because it infected cancer risk assessment principles and practices.

***Fruit flies and a cover-up*** / The story would grow even more bizarre, involving the atomic bomb–making Manhattan Project of World War II. While the Manhattan Project primarily focused on the bomb, it also had a genetics component designed to assess the effects of ionizing radiation on heredity. That work was conducted at the University of Rochester under the direction of world-renowned geneticist Curt Stern. Muller, then at Amherst College, was a paid consultant.

*The flies did not cooperate, showing a threshold reponse in the most extensive study ever conducted on the topic. These findings shocked Stern and his team, threatening to turn their scientific views and world upside down.*

The project included a new fruit fly experiment to confirm Stern and Muller's belief in linearity. However, the flies did not co-operate, showing a threshold response in the most extensive study ever conducted on the topic. The findings shocked Stern and his research team, threatening to turn their scientific views and world upside-down.

Stern and co-author Ernst Caspari did write a manuscript presenting the new data, but they directed the scientific community not to accept or use their findings, even though they came from what was clearly the best study yet done on the subject. A reading of preserved letters and memos between the two and other colleagues reveals their fear that the new findings would invalidate the LNT– single hit model. Their work became an effort to "save the hit model" rather than follow the data.

Five weeks before he received his Nobel Prize, Muller received the Stern–Caspari manuscript. He soon wrote Stern acknowledging the great threat the findings posed for the LNT – single hit model and strongly requested the study be repeated. He also admitted that he could find no problem with Caspari as a researcher or with the study.

Despite the new findings, Muller announced at his Nobel lecture that the threshold model should be trashed and replaced with the LNT – single hit model, knowing full well that a better study did not support that claim. Needless to say, he didn't share that information with his Nobel audience. In effect, this started Muller on the road to deliberate deceit and deception, along with Stern, to ensure the acceptance of the LNT – single hit model.

Muller's public deceptions did not stop with his Nobel lecture. He would publish several dishonest and incorrect articles to further the LNT position, all under the watchful eyes of Stern, Caspari, and others. They simply let their Nobel laureate colleague mislead the scientific community and the general public.

## PANEL PROBLEMS

The 1956 NAS BEAR I Genetics Panel also exhibited some novel, odd, and troubling features.

First, it was not funded by the U.S. Government, but by the Rockefeller Foundation. Second, the president of the NAS was Detlev Bronk, who also was president of the Rockefeller Institute for Medical Research. In essence, Bronk decided to fund himself. Third, he appointed the chair of the NAS BEAR Genetics Panel, Warren Weaver, who was not a geneticist but a mathematician and who had long worked for the Rockefeller Foundation. Weaver had funded essentially most of the genetic researchers in the United States and elsewhere. Fourth, Weaver and Bronk selected the panel and stacked it with LNT believers, clearly ignoring other geneticists with differing views. Fifth, Weaver selected eight geneticists who had no prior publications on the effects of radiation on mutations. Sixth, during a panel session, Weaver tempted panel members with vast sums of research dollars—a seeming bribe. Seventh, panelist James Crow persuaded his colleagues to alter the research record on two specific matters in order to ensure the likelihood of having the LNT recommendation accepted.

LNT would soon become the law of the land, so to speak, and helped to lead the environmental revolution of the 1960s and 1970s. However, Oak Ridge Labs' Russell reported in December 1958 that the BEAR Panel was wrong when it assumed that all ionizing radiation-induced genetic damage was irreversible and cumulative. He convincingly showed that thresholds could occur at low dose rates, probably because of a DNA repair process. That finding shocked Muller and others. Russell's suggestion on DNA repair was confirmed several years later in research that would earn the 2015 Nobel Prize.

These findings set the stage for the next battle. In 1972, the BEIR Committee acknowledged that the 1956 BEAR Genetics Panel had been wrong and that dose rate, not total dose, was the

key factor for mutation and cancer risk assessment. Russell had shown that at an ionizing radiation exposure rate some 27,000 times above the background exposure, female mice showed a clear threshold—that is, no increase in mutations. While the male mice showed a strong trend in the threshold direction in the same experiment as the females, they had not yet achieved the safe threshold dose. Nonetheless, the BEIR NAS Committee retained the LNT model, relying only on the male mice data.

## QUIET REVERSAL

This is where things stood for 25 years, until another Oak Ridge Lab geneticist, Paul Selby (a former student and colleague of Russell), discovered several data problems with the Russell control group. Selby dug into the issue, finding more problems with the research—enough to challenge the key scientific findings. Because of the great sensitivity and significance of these developments, he went to the very top of the Department of Energy and presented his data challenging the Russell findings.

The DOE quietly convened an external panel to evaluate the Selby claims while giving Russell a chance to defend himself. In the end, the panel sided with Selby; Russell had made a major error with his control group data. Russell and Selby both published these revelations in the scientific literature, though they differed on the size of the errors. The corrections were so scholarly written that one could not easily detect the magnitude and significance of the controversy and the underlying hostilities that had emerged. The write-up was amazingly tame and clinical.

These findings sat quietly for another two decades until I came upon them. After obtaining many of the details of the DOE hearing and other information, including a long series of telephone interviews (about 12 hours in total) with Selby, I applied the appropriate correction to the 1972 data used by BEIR to sustain LNT. I found that had the data been corrected at the time of the BEIR I recommendation, it would have supported a threshold rather than the LNT model. Thus, these new findings call into question the "gold standard" that has been guiding U.S. cancer risk assessment since 1977.

## CONCLUSION

The story of cancer risk assessment as told by regulatory agencies such as the EPA is really a profound example of flawed science—the product of errors, deception, perverse incentives from academic grants, and ideology. A major remaining question is whether our regulatory agencies can honestly and objectively confront this history and make the needed corrections, or will they simply preserve the historical "lie" that they and society have long been living. If they do the latter, it will continue the harm to both science and public welfare.

**The proposals before Congress have long-term effects on our nation's budget — and potentially yours.**

**WashingtonWatch.com** delivers the numbers behind federal legislation in the form that matters most: the price for you and your family.

Let **WashingtonWatch.com** be your starting point for investigating what the government does with your money, and for taking action to control it. Whatever your viewpoint, you will have more power to effect change.

Subscribe to the **WashingtonWatch.com Digest**, free e-mail notice of new legislation — and, most importantly, its price tag.

**washingtonwatch.com**

the numbers behind proposed legislation and regulation

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 3/6/2019 12:43:10 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**CC**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Subject**: see link now

https://www.psychologytoday.com/ca/blog/the-gravity-weight/201903/the-scientific-coming-age-old-concept-hormesis

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 3/6/2019 12:40:32 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**CC**: Edward Calabrese [edwardc@schoolph.umass.edu]

Clint:

See this link.

Ed

https://www.psychologytoday.com/ca/blog/the-gravity-weight/201903/the-scientific-coming-age-old-concept-

Message

**From**: Beck, Nancy [Beck.Nancy@epa.gov]
**Sent**: 3/4/2019 12:55:50 AM
**To**: Woods, Clint [woods.clint@epa.gov]; Dunlap, David [dunlap.david@epa.gov]
**Subject**: FW: new paper
**Attachments**: CBI-Calabrese-LNT.pdf

**********

Nancy B. Beck, Ph.D., DABT
Principal Deputy Assistant Administrator
Office of Chemical Safety and Pollution Prevention
P: 202-564-1273
beck.nancy@epa.gov

---

**From:** Edward Calabrese <edwardc@schoolph.umass.edu>
**Sent:** Saturday, March 2, 2019 4:40 PM
**To:** Beck, Nancy <Beck.Nancy@epa.gov>
**Subject:** new paper

Nancy:

See my latest and most comprehensive effort to date on the historical foundations of LNT.

Ed Calabrese

Chemico-Biological Interactions 301 (2019) 6–25

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

# The linear No-Threshold (LNT) dose response model: A comprehensive assessment of its historical and scientific foundations

Edward J. Calabrese

*Department of Environmental Health Sciences, Morrill I, N344, University of Massachusetts, Amherst, MA, 01003, USA*

ARTICLE INFO

*Keywords:*
Linear dose response
Single-hit
LNT
Dose response
Cancer risk assessment
Mutation, ionizing radiation

ABSTRACT

The linear no-threshold (LNT) single-hit (SH) dose response model for cancer risk assessment is comprehensively assessed with respect to its historical foundations. This paper also examines how mistakes, ideological biases, and scientific misconduct by key scientists affected the acceptance, validity, and applications of the LNT model for cancer risk assessment. In addition, the analysis demonstrates that the LNT single-hit model was inappropriately adopted for governmental risk assessment, regulatory policy, practices, and for risk communication.

## 1. Introduction

This paper provides a detailed historical assessment of the origin and progressive development of the linear no-threshold dose response (LNT single-hit model). The time period of this historical assessment starts in 1927 after Muller reported inducing transgenerational phenotypic changes (i.e., heritable mutations) in *Drosophila* via the use of very high doses of X-rays[1] to the present time, with the recent discovery of critical errors made by the U.S. NAS (National Academy of Sciences) BEIR (Biological Effects of Ionizing Radiation) I Genetics Subcommittee (1972) [105] leading to the acceptance of LNT and perpetuating these errors via the subsequent BEIR committees now through BEIR VII. The paper not only details the peer-reviewed literature but also makes extensive use of the personal papers of numerous leading individuals that helped to determine the acceptance of LNT by the scientific and regulatory communities as well as the general public. Despite its standard toxicological analysis framework, this paper also has elements of a scientific detective story with its many unexpected historical twists and turns. This analysis is also different than the traditional scientific review as it documents a disturbing effort by some leaders of the radiation genetics community of the 1940s-1960s to force the acceptance of the LNT model, at almost any cost. Also discussed is the well-documented evidence of deceptions, obfuscations, and deliberate scientific misconduct, all of which significantly affected the broader scientific and medical communities, and regulatory agencies of the U.S., such as EPA, and worldwide. This, in turn, affected cancer risk assessment policies, practices, and recommendations, and had a major impact on environmental regulation, the public health and medical practices throughout the world.

## 2. LNT and biological evolution

The linear no-threshold dose response (LNT) in biology was first proposed in 1928, making it now 90 years old [118]. This idea emerged from a stellar duo of physical chemists from the University of California at Berkeley. The leader was Professor Gilbert N. Lewis, a world famous scientist, who would be nominated for the Nobel Prize some 42 times. However, on this occasion, Lewis would step out of his field and enter the more uncertain, murky and speculative domain of biology, postulating a possible mechanism for biological evolution.[2] Finding the principal mechanism for evolution was perhaps the most fundamental question challenging the biological community in the aftermath of Darwin's Origin of the Species and Mendel's discoveries concerning heredity. The situation created a profound intellectual challenge and great competition within the biological sciences. The search centered on the belief that the answer to the evolution question would be directly

*E-mail address:* edwardc@schoolph.umass.edu.

[1] In December of 1927 at the AAAS meeting in Nashville Muller [85] discussed the possibility that he may not have induced gene mutation but massive large scale heritable chromosomal deletions and aberrations.

[2] This 1928 paper [118] on the mechanism of evolution was preceded by Lewis's 1925 Silliman Lecture at Yale University in which he addressed the broad question of evolution, exploring possible mechanisms. Lewis was therefore predisposed to applying his knowledge of the chemical and physical sciences to the study of evolution.

https://doi.org/10.1016/j.cbi.2018.11.020
Received 20 August 2018; Accepted 26 November 2018
Available online 11 February 2019
0009-2797/ © 2018 Elsevier B.V. All rights reserved.

**Abbreviations**

| | |
|---|---|
| AAAS | American Association for the Advancement of Science |
| AEC | Atomic Energy Commission |
| APS | American Philosophical Society |
| BEAR | Biological Effects of Atomic Radiation |
| BEIR | Biological Effects of Ionizing Radiation |
| CAG | Carcinogen Assessment Group |
| EPA | Environmental Protection Agency |
| ERDA | Energy Research and Development Administration |
| FDA | Food and Drug Administration |
| ICRP | International Commission on Radiological Protection |
| JCAE | Joint Commission on Atomic Energy |
| LNT | Linear No-Threshold |
| NAS | National Academy of Sciences |
| NCRPM | National Council of Radiological Protection and Measurement |
| NEPA | National Environmental Protection Act |
| NRC | National Regulatory Commission |
| PNAS | Proceedings of the National Academy of Sciences |
| RF | Rockefeller Foundation |
| SH | Single-Hit |

linked to how gene mutations were induced and passed on to subsequent generations.[3]

As early as 1910, Thomas H. Morgan had oriented his *Drosophila* laboratory at Columbia University to the study of genes via the pursuit of heritable mutations. However, despite conducting a vast number of experiments designed to 'artificially' induce genomic mutations by a host of noxious chemicals and physical agents, all attempts seemed to fail. A century later this seems hard to believe, since Morgan's group threw nearly everything it could at the fruit fly genome including high doses of ionizing radiation, all without apparent success. This cascading series of experimental failures, while not discouraging future experimental attempts to induce mutation, led to the belief that the genome must be very stable, nearly immutable. Nonetheless, the answer to the "mechanism of evolution" question required finding a means to mutate the genetic material. What was needed was a novel approach. A solution to this challenge was eventually developed by Hermann J. Muller, at the University of Texas at Austin, and former graduate student of Morgan. Muller modified the experimental fruit fly model, making mutations more readily and unequivocally detected.[4] Muller discovered that very high doses of X-rays administered to the male parental generation induced numerous phenotypic changes in subsequent generations, entitling his paper the 'artificial transmutation of the gene'. Muller was very strategic in the framing of the title since mutation of the gene was believed to be the mechanism for evolutionary change. Moreover, while others had previously reported success with the induction of chromosomal aberrations ([53,77–79] [5]), Muller would clearly emphasize that it was the transmutation of the gene that was the fundamental feature of evolutionary change.

The actual data to support Muller's assertions were reserved for a presentation at the 5th International Genetics Congress in Berlin during September (11th-18th) of 1927 [87]. Muller, who inexplicably failed to cite the prior publication of Gager and Blakeslee [53], quickly became an international figure with much public attention. However, the paper containing the data for the major findings was relegated to an obscure conference proceedings [87]. A review of the Muller proceedings paper reveals it lacked an adequate presentation of research methods, cited no references, was sloppy in the presentation of data, and with three experiments, each with study design limitations. An assessment of this publication strongly suggests that this Nobel Prize research was not peer-reviewed [27].[6] Nonetheless, the findings were reproducible, broadly accepted as novel and highly important, principally because of the enhanced capacity to induce what were believed to be gene mutations [168]. In this rush for discovery primacy, Muller [86] acted by publishing his key paper in *Science* (July 22, 1927) three months prior to the Congress, without showing any data. How this occurred was never explained by Muller or the journal nor did the Congress Proceedings [87] paper receive criticism, possibly because others confirmed its basic findings and/or never read it, being content to read the more highly cited, but data-deficient *Science* publication [86]. On April 24, 1928, Muller would make a follow up presentation of his mutation findings, publishing a substantial discussion of the data in the Proceedings of the U.S. National Academy of Sciences (PNAS) on September 15,1928[7] [88].

Inspired by the findings of Muller, Gilbert Lewis and his colleague Alex Olson soon published a follow-up paper in Nature [118], proposing that the mechanism of evolution was genomic mutation induced by cosmic and terrestrial radiation following a linear dose response (they used the term proportional rather than linear). The linear relationship was significant since it would explain observed changes in all species, ranging from least to most susceptible to mutation. The Olson and Gilbert [118] explanation was based on the findings of Goodspeed and Olson [55] [8] on radiation-induced mutation in the primrose plant at a dose some 500,000 fold greater than background.

The LNT model (using the term 'proportional' for linear) was thus first applied to the concept of biological evolution, not cancer/genetic risk assessment. Initially the hypothesis of Olson and Lewis [118] was supported by research of Hanson and Heys [61] from Muller's laboratory and Washington University, who stated that "natural radiation may be responsible for the mutations which are the grist of the natural selection mill with the resulting evolution of new forms." This remarkable conclusion was derived from an investigation of fruit fly mutations in an abandoned uranium mine. Other support for the Olson and Lewis hypothesis was provided by Refs. [46,47,72].

Due to the prominence of the theory of evolution and the reputations of Lewis and Muller, this hypothesis of Olson and Lewis quickly drew considerable attention. However, in the end it failed to gain traction within the genetics and evolutionary biology communities

[3] As early as 1916, Muller would state in a lecture that "the central problem of biological evolution is the nature of mutation …" [39].

[4] Muller's flies had a mutant X chromosome with a crossover suppresser. This was a large inverted segment that blocked the crossing over phenomenon. These flies also had a recessive lethal mutation along with a dominant bar-eye mutation. This permitted the heterozygous females to be visually identified, thereby essentially eliminating an error in phenotype identification.

[5] Gager and Blakeslee [53] would report the occurrence of radium-induce mutation in the Jipson Weed in January, 1927, this being the first report of an exogenous agent inducing gene mutation. This discovery of Gager and Blakeslee [53] has been sustained over nearly a century. However, the findings of Muller [86] simply overwhelmed the field with his far greater capacity to produce mutations. Gager and Blakeslee would occasionally remind the field of their priority while giving credit to Muller for his findings. See Ref. [28] for a discussion of the Gager/Blakeslee and Muller interactions.

[6] A July 8, 1946 letter of Muller to Edgar Altenburg [92] revealed that the paper he read at the 1927 Genetics Congress was published in the proceedings without any change from the presentation text, thus strongly supporting the belief that the key Nobel Prize winning paper was not peer-reviewed [181,182].

[7] Muller [88] cited his Congress Proceedings paper in his PNAS September 15, 1928 paper with the correct page numbers, but with the incorrect year of 1927 rather than 1928. In fact, Muller's PNAS citation was not listed in the basic Web of Science search. This citation was detected in a "cited reference search" of the Web of Science. The 1927 publication date was again used by Muller in a paper by Muller and Mott-Smith [100]. It appears that Muller may have used the 1927 date rather than the actual publication date (1928) to enhance his claim to primacy for the discovery of gene mutation.

[8] The Goodspeed and Olson [55] paper was used since it provided data rather than the "discussional" paper in *Science* by Muller [86].



ED_002751_00030339-00002

since cosmic and terrestrial radiation were only able to account for about 1/1300 of the background mutation rate in the control group fruit flies to what would become the Muller Nobel Prize research using linear modeling [100]. The hypothesis of Olson and Lewis [118] would not be revived, with attention eventually being redirected toward endogenous metabolism with its vast generation of reactive oxygen species (ROS) as a likely mechanistic engine of evolution [43,73].

The reason for the striking failure of the normally highly astute Lewis to discern the problem may have been related to the fact that Muller failed to show any data in his epoch-making *Science* paper, while the proceedings of the 5th International Genetics Congress was published too late and not generally available. As noted above, Olson and Lewis [118] had to rely on the limited findings of Goodspeed and Olson [55]. Thus, it is likely that Lewis was forced to be too speculative in his quest to be the first to offer a plausible mechanism for evolution. A chronology of the history of the LNT is provided in Appendix 1.

## 3. LNT and the proportionality rule

Even though Muller rejected the hypothesis that background radiation-induced mutation acting via a LNT dose response was the mechanistic engine of evolution, he nevertheless would soon accept the validity of the LNT theory and its later linkage with the single-hit mechanism for ionizing radiation-induced mutation and eventually for cancer as well. While it is not yet possible to pinpoint the timing of the adoption of his belief in LNT, it was probably directly linked to the results of two investigations under his direction. It appears that Muller accepted the validity of the LNT for mutation from findings reported in several published studies [57,59–61,115] [89]. Muller had made the assumption that the dose response was linear down to a single ionization event though the **lowest** cumulative dose from these investigations was extraordinarily high, i.e., approximately 285 rads (r), administered at a high dose rate. In contemporary terms, this was roughly the equivalent of receiving 1000 modern chest X-rays in 3.5 min or about five chest X-rays/second. In fact, the lowest dose using the C1B *Drosophila* model in Muller's Nobel Prize research was nearly 6 fold greater than this dose.

While the above papers were commonly cited by Muller as supporting the LNT perspective during this period of concept consolidation, he failed to properly balance and integrate other contemporaneous publications from similar credible studies that did not support the LNT perspective [125,155,175]. Table 1 provides a listing of contemporary radiation-induced mutation studies that supported the LNT/proportionality relationship and those that contradicted it. All of the studies supporting the LNT were conducted at very high doses/dose-rates, hundreds of thousands times greater than background. While Muller remained silent with respect to the challenging studies, he would eventually need to address the issue of cumulative dose, dose-rate, and the nature of the dose response in the low dose zone via improved and more insightful experimental protocols.

The period from about 1927 to 1932 represents the first stage in the historical assessment of the LNT model. While Muller provided the experimental vehicle, Olson and Gilbert [118] created the conceptual framework (i.e., linear dose response) and application (i.e., evolution mechanism), even if those were ultimately rejected. Oliver [115] and Hanson and Heys [59–61] provided evidence to support the occurrence of LNT, even though at extremely high doses/dose-rates. In fact, as this period would come to a close, Muller would transform these developments into no less than a quasi-biological law called the Proportionality Rule, the term Muller used for the LNT concept. The 'proportionality' term was apparently borrowed by Muller from the Olson and Lewis [118] paper, transformed into a 'Rule', which quickly gained standing within the radiation genetics community, but not much further. Table 2 provides a series of citations and a quote within each, showing how the radiation genetics community used the concept of proportional dose response to describe the linear dose response for ionizing radiation and mutation. As described with the quote from Hanson [58] the mutation incidence was directly proportional to dosage and that 'Muller named this the proportionality rule'.

The seminal work of Muller [86] reported for the first time that an external agent, ionizing radiation, could induce gene mutations (i.e., 'artificial transformation of the gene') in the fruit fly genome as inferred from phenotypic changes observed in the next generation. While this was the principal focus for Muller and about which most observers focused, he also directed attention to the concept of dose response, since his Nobel Prize study designs [87] were inadequate to assess the dose-response relationship issue.

Muller's Nobel Prize research initially involved experimentation with a homogenous strain of *Drosophila* females with heterozygous males. In this first experiment he exposed the flies to four 'doses' which were Dose x Duration of X-ray exposures [i.e., 12 (i.e., 810 r total dose over the 12 min), 24, 36, and 48 min]. The two highest doses/durations were quite toxic, inducing sterility in 70–80% of the males. At the lowest dose/duration tested Muller induced a single apparent mutant offspring with a phenotypic change. The phenotypic change rate would increase notably for the 24 min treatment (i.e., 1620 r) over the response of the 12 min exposed group. Choosing not to replicate this four dose/duration treatment study, which suggested the possibility of a threshold at the 12 min duration, Muller switched to his new C1B fruit fly strain, which was a model that gave unambiguous sex-linked mortality results. However, instead of testing over the original four doses, Muller opted to use only the 24 and 48 min duration periods, thereby seemingly attempting to prevent a possible no effect dose at the low end while still maintaining a dose that retained a high risk of toxicity/sterility. This follow up two dose experiment yielded a limited dose response that also was not linear with Muller reporting the increase as a square root function ($\sqrt{2}$) rather than a doubling (2-fold increase) for a linear response.

Follow up research by Oliver [115] using the C1B strain model would be critical in establishing Muller's belief in LNT. In this four dose study the lowest dose tested was sufficiently effective in that it increased mutant lethals by nearly six fold over control values, making a linear dose response. However, when a legitimate challenge to an LNT mutation interpretation was published, as in the case of Stadler [155], it was ignored. For example, Stadler [155] assessed mutagenicity involving 13 radiation doses in barley with the three lowest doses showing no enhanced mutation over the control, reflecting the possibility of a threshold dose response and a challenge to the LNT concept. Despite its enhanced power and greater dose response relevance, such findings were apparently ignored even though Stadler [155], raised the possibility of there being a threshold in his discussion by stating that 'the absence of mutation in the cultures given the three lowest doses might suggest the possibility of a threshold intensity below which mutations do not occur … '.

Stadler would more seriously challenge Muller for the rest of his life (dying of cancer in 1954) over the key assumption that Muller had actually established what he claimed: induced the artificial transmutation of the gene (i.e., mutation) [96,101,127,158,159].[9] While Muller continued to assert that the X-rays induced precise 'point' mutations in single genes (e.g., what today would be called base pair mutations) Stadler [156–158] hypothesized that Muller's mutations were not precise but often, and perhaps totally, manifestations of massive deletions and various genic rearrangements that could involve multiple genes [26]. In contrast to Stadler's description, Patterson and Muller [127] referred to these transgenerational phenotypic alterations as due to 'progressive' mutations/changes, which they argued were the essential foundations of evolutionary change. If Stadler's views were to be persuasive then the

[9] Even after his death, Stadler would challenge the Muller interpretation as his last Ph.D. student Gerry Nuffer [113], who acknowledged the help of Stadler, would publish detailed findings in maize showing no evidence that X-ray-induced transgenerational phenotypic changes were due to gene mutation. He identified a variety of other chromosomal/gene interactions (e.g., position effects) that might account for the findings, thereby challenging the generality of the Muller findings to plant genetics. The challenge of the Stadler/Nuffer findings were broadly applied by others although the authors were astutely careful in their wording.



ED_002751_00030339-00003

significance of Muller's findings would be profoundly diminished, with the results representing a more modest extension of earlier X-ray induced chromosomal (i.e., non-gene) aberration research. While these two titans (i.e., Muller and Stadler) of radiation genetics were unrelenting in their debates (since the stakes were so high) Muller [90] would temporarily prevail (as 'validated' by his Nobel Prize in 1946), possibly due to the power of his personality, and that he outlived Stadler[10] who struggled with cancer over the last eight years of his life. However, once molecular techniques had advanced following the deaths of Muller and Stadler, the data would clearly reveal that Stadler's views were largely vindicated [50,52,111,112,114,123,139,165–167,170]. In contrast, at the high doses used by Muller [86,87] the damage to the mature fruit fly spermatozoa genome would be dominated by massive deletions and other large genetic lesions [117], making the progressive point mutation hypothesis untenable. Reflecting the view that Stadler's interpretations were not only correct but also vindicated can be seen in the judgments of two of Muller's closest radiation geneticist colleagues, Crow and Abrahamson [41]. Nonetheless, the early and widespread acceptance of Muller's far more poorly supported interpretation of the nature of the X-ray-induced genetic damage at high doses would lead directly to the creation of the clearly flawed LNT Single-Hit model.

## 4. Linking LNT with single-hit

By the end of 1932, Muller had developed what seemed to be a firm belief in LNT for X-ray induced gene mutation. However, this belief was without an underlying mechanism or an experimental study in which the protocol would be able to test the legitimacy of the LNT model. These ostensible weaknesses (e.g., very high doses, lack of mechanisms, weak cytogenetic analysis) of the data supporting LNT would be partially rectified by the end of the decade, even if the studies themselves providing the 'rectification' had important limitations. In the case of mechanisms, Muller received a huge boost when he linked up with Timofeeff-Ressovsky, the outstanding Russian radiation geneticist, working in Berlin from 1932 to 1934 and several other international leaders in the physics community such as Neils Bohr, Max Delbruck and Kevin Zimmer. Muller and Timofeeff-Ressovsky would provide some of the key mutational data while the physicists contributed the mechanism, based on X-ray exposure and target theory. While target theory was first developed for use in predicting how chlorine disinfection might kill bacteria (see Refs. [22,36]), it was soon adopted by physicists ([42,130,178]) to explain X-ray-induced mutagenicity. The physicists demonstrated that the more hits needed to produce a gene mutational effect, the more threshold-like the dose responses would appear ([10,180]). In contrast, as the number of hits approaches one, the more linear the dose response would appear (Fig. 1). Thus, the conclusion was judged to be clear. The X-ray induced linear dose response for genomic mutations in the male fruit fly mature spermatozoa was best accounted for with a single hit model using target theory. As a result of this radiation biologist-physicist collaboration, the LNT-Single Hit (SH) model was created.[11] The result of this collaboration was published in 1935 by Timofeeff-Ressovsky and colleagues. Unfortunately, this potentially groundbreaking paper was published in a new journal that was cancelled after only one year, profoundly reducing its potential impact on the

**Table 1**
Dose response mutagenicity data at the time of linearity concept consolidation (Circa 1928–1934) (Source: [13]).

| Reference | | #Doses | | |
|---|---|---|---|---|
| Supportive of Linearity | | | | |
| Oliver [115] | *Drosophila* | 5 doses | X-ray | Lowest dose 275 r |
| Hanson and Heys [62] | *Drosophila* | 2 doses | Radium | Lowest dose 6315 r |
| Hanson and Heys [63] | *Drosophila* | 13 doses | X-ray | Lowest dose 445 r |
| Timofeeff-Ressovsky [169] | *Drosophila* | 5 doses | X-ray | Lowest dose 1400 r |
| Not Supportive of Linearity | | | | |
| Muller [86,87] (Exp 1) | *Drosophila* | 4 doses | X-ray | |
| Muller [86,87] (Exp 2) | *Drosophila* | 2 doses | X-ray | |
| Weinstein [175] | *Drosophila* | 2 doses | X-ray | |
| Hanson [57] | *Drosophila* | 2 doses | X-ray | |
| Hanson and Heys [60] | *Drosophila* | 2 doses | X-ray | |
| Stadler [138] | Barley | 15 doses | X-ray | |
| Serebrovsky and Dubinin [146] | *Drosophila* | 3 doses | X-ray | |

[10] In order to preserve the uniqueness and significance of the artificial transmutation of the gene concept/findings, Muller would publish an 82 page paper in 1930 with his University of Texas colleague J.T Patterson. The focus of the paper centered on whether the X-ray-induced transgenerational phenotypic changes were due to losses (deletions) and rearrangements of portions of chromosomes or rather the so-called "progressive" point-like, genetic changes that he believed drove evolution. This article, in many ways, reflected the pattern of Muller's professional life. He marshaled as much evidence as possible, presented it in excruciating detail and never compromised on an essential point knowing in advance that he had to defend the artificial transmutation of the gene concept [26]. What then was the basis of his belief that he had induced intra-genic (i.e., "real") mutations. The cited reasons for this belief/conclusion included: (1) the general randomness and specificity of induced phenotypic changes (called mutations); (2) identical phenotypes were independently affected; (3) that phenotypic changes were dose dependent; (4) that numerous toxic chemicals were not effective in producing such changes and (5) (similar to 4) "most important of all, probably, is the fact that a direct and simple proportionality has been shown to exist between the frequency of the induced mutations and the amount (energy) of the radiation absorbed." Patterson and Muller [127] cited Hanson and Heys [60] and Oliver [115] to support this conclusion. Patterson and Muller [127] then stated that "there is no indication in the results of any lower critical intensity, or threshold value, beneath which there is no (or a relatively lesser) effect." In the body of the paper Patterson and Muller [127] would also emphasize that X-rays could on occasion induce reversible changes such as white eyes to red and the reverse, supporting a view that relatively modest phenotypic changes could be induced that reflected normal "spontaneous mutations". The problem with the Muller argument was that it was based on logic, inference and parsed arguments. Missing from his views was actual proof concerning the nature of the radiation-induced genetic lesions over the tested dose range. Thus, from 1930 to the mid-1950s the Stadler and Muller perspectives would collide, awaiting advances in methods that would permit determination of the nature and size of genetic lesions. Of importance was that Painter [130–132] provided novel cytogenetic staining techniques for *Drosophila* chromosomes based on the earlier work of McClintock [80–82] for corn. These techniques would clearly show that the X-ray treatments used by Muller produced a very high level of chromosomal aberrations, weakening his point mutation argument. The reverse mutation explanation offered by Muller was also refuted in multiple studies (e.g., [70,71,174]. Additional methodological advances would emerge with the development of the Southern blot [153] and PCR a decade later [102]) which further supported the Stadler position.

[11] The mutational effect was viewed as being caused by one or a few discrete, basic biophysical effects, which were conceived to be "hits" on a "target". The genetic mutation was assumed to be a "pure physical event" with no physiological or biological involvement [173]. From a range of ideas as to what constituted a hit, it was possible to then derive statistical models of dose-responses. If only a single hit on a single target was needed to induce the effect, with the percentage rate of the effect graphed on a logarithmic scale, the dose response would appear then as a straight line. The various mathematical model predictions were then compared to actual data in the dose-response studies. The visual confirmation of the emerging theory with actual mutagenic dose response data made the LNT single-hit model believable and readily accepted. This process led Timofeeff-Ressovsky et al. [169] to assert that gene mutation was a "one-hit" process, caused by a single ionization from a quantum of radiation on a sensitive region of the genome. They even went so far as to estimate the physical features of a sensitive region, it being about the size of a large organic molecule [10].



ED_002751_00030339-00004

**Table 2**
Documentation of the introduction of the proportionality rule concept into the mutation literature, 1929–1960 (Source: [17]).

| References | Quotes |
|---|---|
| Hanson and Heys [60] | "It is only to be expected that the number of mutations be directly *proportional* to the number of rays to which the organisms are exposed." Page 207 |
| Muller [89] | "Since then Hanson, using radium, and Oliver in our laboratories using X-rays, have both found that the frequency of mutations produced is exactly *proportional* to the energy of the dosage absorbed ... There is, then, no trace of a critical or threshold dosage beneath which the treatment is too dilute to work." Page 236 |
| Oliver [115] | "That is there is a direct *proportionality* between the percent of lethals and the length of time of treatment may be seen more readily by a comparison of the t1 values calculated from the results for each of the given doses." Page 45 |
| Stadler [155] | "Mutation frequency increased approximately in direct *proportion* to dosage." Page 13 |
| Hanson and Heys [63] | "Taking the amount of ionization in air as a measure, the mutation rate seems to vary approximately in direct *proportion* to the intensity." Page 142 |
| Oliver [116] | "By inference it can be added that the cosmic and the terrestrial radiations of higher energy content also are capable of producing mutations in *proportion* to their power of ionization." Page 480 |
| Oliver [116] | "The relation of *proportionality* to the dosage applies not merely to the lethals in general, but, more specifically, to the lethal gene mutations." Page 485 |
| Oliver [116] | "... [gene mutations and gene rearrangements] ... all probably occur in direct *proportion* to the dosage, no matter how small a dose is used." Page 486 |
| Patterson [126] | "In general their results [i.e. [59,115]] justify the conclusion that the rate is directly *proportional* to the dosage employed." Page 133 |
| Hanson and Heys [62] | "Further evidence of the *proportionality rule* from a study of the effects of equivalent doses differently applied." Page 335 |
| Hanson and Heys [62] | "Experiments planned with a view to determining within what limits the *proportionality rule* holds show again a strict correspondence existing between the amount of radium administered and the consequent biological effect, the induced mutation frequency obtained varying directly with the dosage." Page 343 |
| Hanson [58] | "The rate seems to be directly *proportional* to the dosage. Muller has named this the '*proportionality rule.*' For example, when all other factors are kept constant, doubling the time of exposure also doubles the number of lethal mutations." Page 486 |
| Oliver [117] | "The frequency of induced mutations is directly *proportional* to the intensity of the treatment." Page 391 |
| Delbruck [44] | "The *proportionality rule* gave the basis for the single-hit interpretation ..." Page 359 |
| Stern [161] | "The *proportionality rule* has been proven to hold over a wide range. Figure 155 shows that, for Drosophila, the relation is essentially linear over the range from 25 r to several thousand r. It has further been shown that the frequency of induced mutations is independent of the time over which the radiation is applied." Page 433 |
| Stern [162] | "It has been established for a variety of experimental organisms that the number of mutations induced by radiation is proportional to the dose. This *proportionality* has been proven to hold over a wide range of dosages." Page 491 |

scientific community. The obscurity of the Journal and the fact that it only lasted one year, prevented the paper from citation in leading indexes, creating what would have been a virtual academic death sentence had these authors not been so prestigious and professionally connected. Nonetheless, Muller's Proportionality Rule now had a potential mechanism that could account for its findings and a new name: Linear-No-Threshold (LNT) single hit model.

## 5. Dose-rate and LNT

While the professional disputes between Muller and Stadler over transgenerational phenotypic changes and mutations were significant, acceptance of Muller's gene mutation view was essential for the development of the LNT single-hit dose-response model. It is now known that the lowest doses employed by Muller in his Nobel Prize research induced massive deletions throughout the genome with many probably approaching and exceeding 100 kb (kilobase) size along with other major genetic alterations [50].[12] The physical deletion of large chunks of DNA, damaging dozens to multiple hundreds of thousands of nucleotides, affecting numerous genes in large numbers of cells, as well as inducing substantial inflammatory responses within and between cells, is not compatible with the basic features of the LNT-SH model as described by Timofeef-Ressovsky et al. [169]. Despite the fact that modern advances [69,139] refuted the single-hit interpretation by Timofeef-Ressovsky et al. [169], these critical insights have only recently been used to reassess the validity and historical foundations of the LNT single-hit model [24–26].

The scientific basis for the LNT single-hit theory as developed by Refs. [86,169] and others was improperly framed, based upon incorrect assumptions, lacking essential understanding of induced genetic damage and its biological significance. Thus, from a theoretical basis, the LNT single-hit theory-model represented a type of biological reach that was excessively ambitious, lacking credible genotoxic information required for the development of a mechanistic model for risk assessment/regulatory purposes. Yet, despite such serious limitations, the LNT findings would be integrated with the one-hit mechanism; it was easily understood from a conceptual perspective and would be later readily (if uncritically) adopted by governmental regulatory agencies.

While the LNT single-hit model was a key step forward, its credibility remained limited, having only a descriptive high dose experimental basis requiring substantial extrapolation from high to low dose and a mechanism that was expressed with mathematical simplicity through experimental validation at low doses. Despite such multiple challenges coupled with the lingering and documented doubts of Stadler and others, Muller would eventually develop a way to attack the model-validation question experimentally.

This new experimental approach was based on the assumption that X-ray induced mutations were cumulative and irreversible. Under such a set of conditions, it was predicted that the total/cumulative mutation damage would be the same regardless of whether the dose of radiation was given acutely or spread over a prolonged period of time. It is not clear where Muller first got this idea but the concept was similar to the Bunsen-Roscoe Law (1862) and Haber's Law [12,84,176,177] both of which described a type of Concentration X Time = Constant relationship. Several references relating to application of the Bunsen-Roscoe Law were available to Muller and his graduate student Ray-Chaudhuri in the years leading up to the research and may have influenced them [68,143,160]. The Bunsen-Roscoe Law has been referred to as the 'Reciprocity Law', discovered by the famous chemist Robert Bunsen and his colleague H. Roscoe in 1862. This 'law' indicates that the amount of product of a photochemical reaction is the result of the total amount of radiation energy hitting the photochemical system, in effect, an intensity x time formulation. The strengths and limitations of Haber's Law had been broadly assessed but usually within the framework of inhalation toxicity, not radiation genetics, or dose-genomic mutation incidence. When Muller became the advisor of Ray-Chaudhuri at the University of Edinburgh in the late 1930s, this new experimental dose-time framework became his dissertation area, working with mature

[12] If Painter's cytogenetic staining of *Drosophila* had been available a decade earlier so that the extensive X-ray induced damage to chromosomes of Muller's fruit flies in 1927 were better appreciated, it may have averted the development of the LNT Single-Hit theory. However, by the time Painter had published his findings, the Timofeeff-Ressovsky et al. LNT Single-Hit model concept was well on the way to being finalized.



ED_002751_00030339-00005

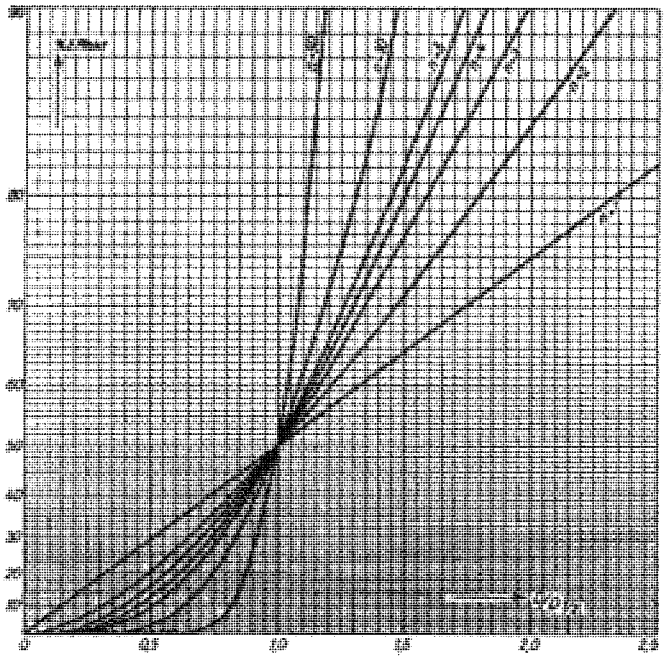


**Fig. 1.** Model dose-response curves, calculated theoretically for various number of "hits," n on a single "target" assumed necessary to produce the effects (From [180]).

male fruit fly spermatozoa. Ray-Chaudhuri would cite the Bunsen-Roscoe Law as the theoretical framework for his research on the dose-intensity x time relationship [131,132]. The most likely reason for citing the Bunsen-Roscoe Law rather than Haber's Law was that several papers had been reported on the effects of X-rays on biological end-points based on the Bunsen-Roscoe Law, whereas Haber's Law had yet to be applied in such a manner.

Using the Muller fruit fly model [132], Ray-Chaudhuri obtained data that provided support for the LNT hypothesis for radiation-induced mutagenicity based on the mature male spermatozoa, all with a quantitative model that appeared theoretically sound. An important problem remained however, since the research of Ray-Chaudhuri had critical limitations. In general, these problems included inadequate control groups, acknowledged major statistical errors by this Ph.D. Committee [56], and issues with experimental quality control features, some of which were recognized by Caspari in correspondence with Stern (American Philosophical Society [3,4]). In specific terms, the Ray-Chaudhuri study was of modest size and lacked the reporting and documentation of multiple essential methodological parameters. The paper also did not include data on lethal clusters, the occurrence of female sterility and fertility, sex ratios, as well as the age of the males, and other factors. He also made a decision to change to a different fruit fly strain midway through the set of experiments, a decision without any explanation. Of significance was that the new strain displayed a control group mutation incidence of approximately one third of the strain it replaced. Yet, Ray-Chaudhuri simply combined the data of the different strains claiming there were no strain differences. None of these limitations were noted by Professors Haldane or Muller in their written assessment of Ray-Chaudhuri's dissertation (Ray-Chaudhuri material – Muller File, Lilly Library, Indiana University). Furthermore, in letter exchanges between Ray-Chaudhuri and Muller, it was clear that Muller was not present for most, if any, of his experiments due to travel, failing to offer crucial, timely and hands on guidance (Muller to Ray-Chaudhuri, Muller File, Lilly Library). Nonetheless, all these weaknesses were carefully submerged, as Muller was seemingly intent on using the Ray-Chaudhuri study to promote the LNT in the face of much skepticism. In fact, Muller [90] would use the Ray-Chaudhuri data to promote the LNT model in his Nobel Prize Lecture.

Muller would frame the dose-rate study of Ray-Chaudhuri as a possible game changer. However, this would not be the case if the experimental limitations could not be overcome. In fact, the soon to be initiated Manhattan Project mutation studies would provide such an opportunity. Muller once again found himself involved, this time as a paid consultant with Professor Curt Stern at the University of Rochester. The research was to evaluate the effects of X-rays/gamma rays on fruit flies, with the intent of assessing the nature of the dose response and dose-time response for transgenerational genomic mutations. That is, Stern was going to assess whether linearity at low doses occurred, making use of Muller's dose-rate methodology, and the Muller-5 strain of fruit fly. This study would be a far stronger one than Ray-Chaudhuri's with respect to technical capacity, study design, sample size, statistical power, quality control, professional supervision, and at a dose rate approximately 1/6 of the Ray-Chaudhuri studies.

## 6. The Manhattan Project: testing the LNT hypothesis

One component of the Manhattan Project assessed whether the dose-response for mutagenicity induced by ionizing radiation was linear via a total dose/dose-rate experimental protocol using the fruit fly. Those associated with the study expected the X-ray-induced mutations to be independent of dose-rate, and explained by the total dose received based on the Ray-Chaudhuri [131,132] findings. However, a significant problem occurred when Ernst Caspari, who was conducting the chronic exposure part of the research, reported to Stern in August 1946. His findings not only did not support the total dose hypothesis, but also displayed a threshold, showing a tolerance dose [14]. These findings were potentially important since they challenged those of Ray-Chaudhuri [131,132], which in turn had been used as key foundational support for the LNT. As noted above, the Caspari study had much going for it. In fact, the integration of the Spencer/Caspari experiments combined to yield a dose-rate study that was designed to 'settle' the dose-rate question that the Ray-Chaudhuri report initiated.

Upon learning of the Caspari chronic experimental data, which supported a threshold and/or tolerance dose, Stern refused to accept the findings as valid, claiming that the problem was not with the dose-rate and linearity hypotheses but with Caspari's control group. This involved Stern's claim that because mutations in this control group were aberrantly high it would lead to the absence of a treatment effect, and show a false threshold dose response [5].[13]

What eventually evolved in response to the Caspari/Stern dispute would be both surprising and historically significant. Caspari refuted the claims of Stern by showing that his control group was consistent with the published literature, forcing Stern to withdraw the criticism [5]. However, Stern (and perhaps with Caspari's consent) wrote in their discussion of the manuscript that the strikingly new threshold supportive findings should not be accepted until it could be determined why these results seemed to conflict with the acute data of the Spencer experiment [154]. A problem with this position was that the Spencer and Caspari studies used significantly different methods and it was not practically possible to resolve their divergent results (see Table 3 for differences). Stern seemed, however, very comfortable accepting the methodologically inferior Spencer report [154] rather than the threshold-supporting findings of Caspari.

Stern asked Muller to review the now drafted Caspari manuscript just prior to his Nobel Prize trip/lecture. Muller acknowledged its receipt and commented on it in a letter to Stern (November 12, 1946 - [91]) stating that these findings (1) challenged the current LNT dose-response paradigm, (2) needed to be replicated, and (3) that Caspari was a competent researcher and he would not dispute his research findings. Despite such a written statement just prior to his Nobel Prize,

[13] See Calabrese [14] for a detailed, point-by-point discussion of this dispute.



ED_002751_00030339-00006

Muller would go on to claim in his Nobel Prize lecture that there was no scientific evidence to support even the possibility of a threshold dose response. The only option he insisted that was possible was the linear dose response. He believed there is 'no escape from the conclusion that there is no threshold dose' (Nobel Prize lecture, HJ Muller, December 12, 1946). The above described sequence of events suggests that scientific certainty about this key issue had devolved into a belief system.

The Caspari and Stern draft manuscript sent to Muller on November 6, 1946 contained the following sentence in the conclusion: 'From the practical viewpoint, the results presented open up the possibility that a tolerance dose for radiation may be found, as far as the production of mutation is concerned'. This statement of Caspari and Stern ([31]- page 15) which was sent to the AEC archives and to Muller, made it clear that Caspari and Stern believed that a threshold for ionizing radiation induced mutation was 'possible'. In fact, the only changes in the entire paper after Muller's review was the elimination of this sentence in the summary and the addition of Muller's name in the acknowledgement section. These insights into Muller's dynamic intervention with the Caspari and Stern manuscript reflects that both Stern and Caspari believed that a threshold interpretation best applied to their mutation data. Yet, Muller would inexplicably override this possibility, while recommending replication of the study in private communications with Stern [Muller Letters to Stern - November 12, 1946 [91] and Jan 14, 1947 [93]]. The conflict that Muller had with the Caspari data became obvious. How he dealt with it became problematic.

We see that Muller not only had a strong belief in the LNT but a profound bias as reflected in his misleading and deceptive comments at his Nobel Prize lecture. Muller would go on to repeat the original criticisms of the Caspari work [94,95],[14] relating to the control group while Muller's own research produced copious data indicating that the Caspari control group data was fully consistent with his own data and the published literature [19].

The situation became more complicated when Stern tried to replicate the Caspari findings from the fall of 1946–1948, now working with a new graduate student, Delta Uphoff. The first major experiment by Uphoff was problematic, as it appeared that the control was aberrantly low, about 40% below normal. Having just gone through the Caspari control group dispute, Stern needed to get the control group issue settled. He then entered into a series of letter exchanges with Muller on the topic, focusing on the Caspari and Uphoff data. Since Muller was extensively researching control group spontaneous mutation variability with the same model (in his continuing dispute with Stadler over gene mutation), he was in an ideal situation to inform Stern. In these letter exchanges Muller was highly supportive of the Caspari data.[15]

As a result of this evaluation, the Uphoff data were viewed as 'uninterpretable' as Uphoff and Stern [171] wrote in a then classified full-length manuscript for the Atomic Energy Commission (AEC). Further complicating the matter, these authors (Stern and Uphoff) blamed the problem on 'investigator bias' (i.e., 'may reflect a personal bias of the experimenter') in the discussion of the paper without explaining what this meant and who was to blame for the bias, as well as whether such bias affected other ongoing experiments and staff, and how Caspari's study would be interpreted. The second of the replication experiments of Uphoff would also yield a similarly aberrant low control group, thereby making two major experiments uninterpretable. The final Uphoff experiment was also problematic, not because of the control group, but because the low dose radiation treatment induced mutations that exceeded predictions of the LNT model by several fold [14].

With World War II over, the Atomic Energy Commission (AEC) needed to have reliable data to guide it on the assessment of the health effects of low doses of radiation. The AEC had invested in mammalian and insect (i.e., fruit fly) studies at the University of Rochester. In the case of the mammalian studies as lead by Professor Donald Charles, no effective guidance was forthcoming. This was believed to be due, at least in part, to the well-known and highly frustrating reluctance of Charles to release/publish his findings unless fully confident with the experimental results. Even after the use of over 400,000 mice, little of value was shared with the scientific community by that group. This included a brief, three-page summary in 1950 [34], some five years after the war ended. By 1954 with no follow-up publication, Charles had resigned from the University and a year later he committed suicide [6]. A summary paper was eventually published in 1961 that was far too late [35], as these efforts had been surpassed by the striking research findings on dose-rate using the mouse model by William L. Russell as discussed below.

For differing reasons, Stern was also being challenged to produce results. In his case, the problem was that each large experiment had a significant concern or flaw as discussed above. Refusing to accept the idea that his research would not achieve the stated goals, Stern decided to rehabilitate the uninterpretable (and experimenter biased) data of Uphoff and to re-marginalize the findings of Caspari, without sharing the detailed 'inside' story validating the Caspari control group as described earlier. This resulted in Uphoff and Stern [172] publishing a one page technical note in *Science* summarizing all five major experiments (i.e., Spencer, Caspari and three by Uphoff), integrating them to claim support for the LNT. They promised the *Science* readership a subsequent highly detailed paper with all the necessary methods, materials, and data. However, they failed to fulfill this pledge. Nevertheless, lacking supporting data the *Science* paper became highly influential, propelling the acceptance of LNT, even though there is no evidence that Stern's radiation geneticist colleagues ever requested the detailed follow-up paper.

### 6.1. Facilitating the acceptance of LNT: role of Rockefeller Foundation and the National Academy of sciences – the BEAR I Genetics Panel

During the early 1950's aboveground testing of nuclear weapons led to increased worldwide exposure to various radionuclides prompting public health concerns. This would lead to the Rockefeller Foundation (RF) funding the U.S. NAS to undertake a detailed assessment of multiple areas of concern (i.e., oceanography and fisheries, meteorology, waste disposal and dispersal, agriculture, pathology, and genetics). The President of the Rockefeller Institute for Medical Research (later renamed Rockefeller University) as well as the President of the National Academy of Sciences (NAS) at that time was Detlev Bronk. In reality, therefore, Bronk was responsible for funding some of his activities as President of the NAS. In this dual role, Bronk selected Warren Weaver, a mathematician, and the long-term scientific director of the RF, to chair the NAS Biological Effects of Atomic Radiation (BEAR) Genetics Panel. Furthermore, Weaver knew most, if not all, of the BEAR I Genetics Panel members, and had long funded some of them such as Sonneborn and Muller, contemporaneously, during the time of the Genetics Panel proceedings. As reported by Wynchank [179], prior to the creation of the Genetics Panel, the RF had funded close to four million dollars to the University of Indiana for research in the area of radiation genetics alone.

At the start of the BEAR I Genetics Panel Weaver showed his power

[14] In footnote 1 on page 10 of [94] Muller stated that "Uphoff and Stern have published a report of further work, with doses as low as 50 r, given an intensity as low as 0.00165 r per minute. The results obtained are entirely in conformity with the one-hit principle. A consideration of these results, together with the early work, leads to the conclusion that the deviation first referred to (the Caspari and Stern [32] findings) was caused by a value for spontaneous mutation rate that happened to be unusually high." Muller [95] would continue his discredited criticism of the Caspari and Stern [32] paper, repeating the "unusually high control frequency" (page 476) conclusion as a basis to reject its challenge to linearity. These statements of Muller complemented the deceptions of Stern, thereby further enhancing the acceptance of LNT while also preventing his deceptive remarks at the Nobel Prize lecture from being discovered.

[15] See Appendix A, Calabrese [16] for a set of the Muller-Stern exchanges.



ED_002751_00030339-00007

over funding support by stating that he would 'try to get a very substantial amount of free support for genetics if at the end of this thing we have a case for it. I am not talking about a few thousand dollars, gentlemen. I am talking about a substantial amount of flexible and free support to geneticists' ([104]; BEAR I Genetics Panel Transcripts February 5, page 35). This is a significant statement as it had the intention of encouraging Panel members to align their recommendations with what the RF believed was important if they wanted to continue to receive Foundation funding. Weaver would further contextualize his funding remarks with the statement: 'There may be some very practical results – and here is the dangerous remark – don't misunderstand me, we are all just conspirators here together'. Weaver's comments are unambiguous, linking project outcomes to RF funding interests and the needs of the radiation geneticists of the Panel.[16]

At the time of the convening of the BEAR I Genetics Panel, the threshold model guided U.S. government policy for assessing risks for both non-carcinogens and carcinogens. Members of the radiation geneticist community, as lead by Muller, had long challenged this view hoping to change it to a proportionality/LNT model. However, on multiple occasions on national and international advisory committees, radiation geneticists had failed to be sufficiently persuasive, never having the votes to replace the threshold with the LNT model. This was principally due to the fact that these Advisory Committees were dominated by persons trained in medicine rather than radiation genetics. This situation would change by design of the RF, via Bronk and Weaver. They made sure that there would be a distinct Genetics Panel that would be separate from a Medical (i.e., pathology) Panel and the RF would uniquely highlight and distribute its findings via multiple, highly visible and influential venues. This is really all it would take to affect a change in national policy for the next six decades.

I was interested in reading the meeting transcripts of the BEAR I Genetics Panel, seeing a substantial debate between proponents of the threshold and LNT models. While I knew that LNT had won the dispute, I wanted to see how these experts debated, which arguments dominated, and which geneticists were most persuasive. My expectations were far too high. As it turned out there was no debate. What happened early on in Panel activities was that Tracey Sonneborn, Muller's colleague at the University of Indiana, read into the record the equivalent of the Radiation Geneticist Mantra, indicating a belief that all radiation-induced mutational damage was cumulative, irreversible, and lacking repair. This combination of factors led to their belief that the dose response for radiation induced mutations was linear down to a single ionization. Radiation genetic risk assessment was best explained based upon the total dose; dose-rate, regardless of how low, would only result in cumulative damage. Sonneborn was not challenged on any point. This was a curious situation since most of the members of the Panel were often opinionated, at times had disputes with each other, and sometimes these interpersonal disputes were rather inflammatory. For example, Muller resigned from the editorial board of Advances in Genetics in a dispute with Demerec, the Editor-in-Chief, over publication of a manuscript by Ref. [33]. Demerec accused Muller of attempting to impose his version of scientific censorship [45]. Yet, despite their apparent personal rift, they were in full agreement on LNT.

Since the BEAR I Genetics Panel was in agreement that the dose-response was linear for radiation-induced mutagenicity it soon found itself with little to do. To fill this void, Weaver challenged the geneticists on the Panel to independently provide their detailed written estimates (including methodology) concerning the number of genetic defects the American public would experience assuming the gonads received a specific dose of ionizing radiation. This genetic damage was to be estimated for the next ten generations. Since the Panel was comprised of a broad range of geneticists (e.g., bacterial, paramecium, fruit fly, mammalian, clinical, population-based, etc.) each was encouraged to use their own education, training, and research methods to derive their independent answers. It was felt that if the estimates of harm from such divergent, but complementary perspectives closely converged, it would enhance confidence in policy recommendations.

Following their meeting on February 6, 1956, the Panel members were expected to complete their analyses over the next month. Of the 12 geneticists on the Panel (i.e., there were 13 to start but one resigned due to academic obligations), nine took up the challenge and provided detailed separate reports within the next month. The other three Panelists declined to submit comments, principally because they believed there was too much uncertainty such that any estimates would not be reliable. In the case of the human geneticist, James Neel, at the University of Michigan and expert on the effects of the atomic bomb on Japanese survivors, he was particularly animated in asserting his position based on written correspondence with Weaver. Neel believed that the uncertainty would be so substantial that it would be unethical to even provide them. More specifically, Neel wrote to Weaver the following on April 17, 1956:

> "The geneticist has social responsibilities, but he also has the responsibilities as a scientist. One is that in an area as critical as this one is, he must beware of letting his conjectures get too far in advance of his facts. It is to me an exceedingly tenable position, having stated the general genetic argument, to say flatly that we know so little about the quantitative aspects (see Ref. [20])."

The letter once again reflected the opinion of Neel that providing population-based estimates of genetic damage was an indefensible exercise and that he would oppose doing such that 'he would go down with flags flying and guns booming to the last' [108].

When the nine separate assessments were received, they were given to Jim Crow to collate, organize, and summarize so that the Panel could more easily assess the submitted reports (his specific function was 'to go through all the damage estimates, compare them, and display assumptions, methods, input, and results in some sort of chart or graphic form'. [20]; page 4). Upon his initial review of the received estimates, Crow sent a letter to Weaver on March 7, 1956 [37] stating the following:

> "Upon looking at the estimates I realized two things. One is that nobody seems to have very much confidence in them. The second point is that those who arrived at comparable estimates usually did it by comparable procedure so that they are not very independent."

Less than one week later Crow again wrote to Weaver [March 12, 1956 [38]]. 'The groups differ widely in their confidence in the best estimate, as indicated by their grossly discrepant minimum and maximum estimates.' In a follow up March 29, 1956 letter to Weaver [39], Crow wrote, 'The limits presented on our estimates of genetic damage are so wide that the reader will, I believe, not have any confidence in them at all.' That is, even though the expert radiation geneticists were told to assume that the dose response would be linear (thus already restricting group variability), the estimates nonetheless profoundly varied. The degree of disagreement was so substantial that Crow asserted that if these values were shared with the scientific community and the general public that it was likely that the Panel's scientific and policy recommendations would have little credibility. This was the key

[16] Obtaining grants to support research was important to some NAS BEAR Genetics Panel members. Personal Correspondence of some of the BEAR Genetics Panel members reveals they were motivated, at least in part, by self-interest, to overstate public health risks to promote their scientific and personal/professional agenda [18]. The fact that distinguished radiation geneticists of the BEAR Genetics Panel may have been willing to exaggerate risks (i.e., be dishonest - in their words: "stretch a point") to enhance their chances to obtain funding, is a critical finding as this type of self-interest has been usually only applied to scientists funded by private interests. What the comments reveal is that academic researchers who are dependent on government/foundation grants may be similarly susceptible. In the present case, these findings may be profoundly significant as the switch to the LNT model had major public policy implications.



ED_002751_00030339-00008

**Table 3**
Differences between Spencer/Stern and Caspari/Stern [32,154] (Source: [14]).

| | Spencer/Stern | Caspari/Stern |
|---|---|---|
| Exposure | X-rays | Gamma rays (radium needle) |
| Animal Model | Males exposed prior to mating | Females exposed after mating |
| Exposure Duration | Acute exposure (minutes) | Chronic exposure (21 days) |
| Dose Rate | ~15,000-fold greater than Caspari | ~1/15,000 of Spencer |
| Vials | Plastic vials to hold flies | Glass vials to hold flies |
| Temperature | 24 °C | 18 °C |
| Diet | Cornmeal molasses | Honey yeast agar |
| Age (males) | ≤7 days, most 2–4 days old | ≥5 days |
| Controls | Controls poorly matched with treatment exposure period | Controls closely matched with treatment exposure period |
| Temperature Control | Poor, highly variable based on external conditions | Good |
| 50-r Treatment Group | 2 groups with different dose rates and exposure period all combined | A single 50-r treatment group all treated similarly |
| Mold Control | Used Moldex throughout study | Possibly less Moldex used in the 21 day radiation exposure period due to the lower temperature (18 °C vs. 25 °C) |
| Lethal Clusters | Not corrected for lethal clusters. If so, the treatment group (50 r) used would have had its mutation rate decrease by −8% versus 4% for controls. | Corrected for lethal clusters. No differences between control and treatment |
| Control/Background Radiation | Background exposure not given | Background exposure reported as 0.6 r |
| Sample Size Comparison | 50-r treatment group had 20,400 less flies than the Caspari experiment | |
| Study Design | The study was not designed to affect the occurrence of lethal clusters | The study was designed to minimize the possibility of lethal clusters |
| $F_0$ Breeding Protocol Differed | 40 females/40 males; females – 2 days old | 50 females/100 males; females ≤16-h old |
| Radiation Exposure Condition Differed | 20 males/capsule; no food in capsule | 50 females/capsule; food in capsule |
| Lethal Designation Protocol Differed | Used 6 heterozygote females in $F_2$ generation to identify lethality | Used 2 female heterozygotes in $F_2$ to identify lethality |
| Viability criteria | A single wild-type male offspring lead to a designation of viable culture. | A single wild-type male offspring lead to a designation of a semi-lethal. |

factor for Crow and the entire Panel. The assessment by Crow of the profound disagreement in the estimates amongst the participating nine geneticists would now be seen against the backdrop and context of the Sonneborn statement:

> … "the thing of most value in all this calculation would be to show how one can use different methods to make estimates, and see to what extent methods, if possible, variations in approach, lead to different answers. So that if they converge, or tend to converge, then we might have more willingness to put them forth." (BEAR I Genetics Panel Transcript, page 257)."

The problem of a lack of genetic damage estimate convergence by the panelists came to a head. There was really no way to proceed with confident recommendations. Further, these 'discrepant' estimates would have been even more discrepant had the views of the three non-participating geneticists, such as Neel, somehow been integrated into overall analysis. So what was the next step forward?

Without having the authority or having been so instructed to do so, Crow decided to save the 'single-hit theory', like Muller and Stern did a decade earlier. Crow excluded several of the independently provided expert assessments. This action was taken despite the fact that each of the Panel members was considered a legitimate world-renowned geneticist with a unique area of specialization.[17] Crow made the decision to eliminate the contribution of Demerec based on bacterial estimates. This action was taken for the stated reason that Demerec's values differed the most from the other estimates due to the use of different methods and approaches. More specifically, Crow wrote to Weaver on March 12, 1956 [38] stating, 'I haven't included Dr. Demerec's estimate on the graph for it, too, is based on quite different assumptions that lead to a greatly different value than the others obtained.' The bottom line is that Demerec's estimate of genetic damage was far below the other eight expert estimates and added significantly to the lack of desired convergence that Sonneborn emphasized was necessary.

The diversity and complementarity of approaches for the genetic damage risk estimates had been deemed to be a key strength of this exercise. However, upon seeing the results, Crow now thought otherwise and eliminated the human population based estimates of Wright and Kaufmann, without justification. The Wright and Kaufmann estimates were the next to lowest estimates. Given that Crow repeatedly expressed concern about the substantial variability amongst damage estimates of the panelists it was not surprising that the three estimates that he eliminated were the lowest. By eliminating these three from the total, it markedly reduced the range of the 'discrepant' estimates.[18]

The actions of Crow to eliminate three expert estimates and the willingness of the Panel to follow his lead is striking. In many ways, this situation became perversely humorous, especially after reading the basis of Crow's personal 'expert' estimates. For example, consider the methodology of Crow, which, of course he accepted. Crow combined three methods to provide a 'best' estimate of genetic damage, including his version of upper and lower bounds. He first decided to use data from the fruit fly for a lower bound. He then decided that human risks from the Japanese bomb survivor data would comprise the upper bound. The 'best' estimate was the mouse data of Russell since it rested conveniently between the fruit fly and human data. While each of these biological models may be used to construct their own best estimate and upper and lower bounds of uncertainty, the integration of each of the models as described by Crow is strikingly inappropriate. The bizarre manner in which he did these was amateurish and revealed that Crow had little understanding of how to proceed. Yet, there is no record that this approach was criticized by any member of the Panel. Further, Crow had stated that his actions to eliminate the estimates of Demerec,

[17] There is a strong general impression/belief that the BEAR I Genetics Panel members were top experts on radiation genetics, based on experience/publication record. In fact, the majority of the geneticist panel members had never published an article on radiation induced mutations prior to their selection on the Panel. Several others had a limited (i.e., several papers) publication record in this area. The bottom line is that the "expert" Panel image was a myth created by the Rockefeller Foundation and U.S. NAS to enhance the acceptance of the policy recommendations of the final reports.

[18] The best estimates of genetic damage for these three eliminated geneticists was: Kaufmann – 195,000; Wright – 50,000; and Demerec – 5220. These collective estimates are approximately 70% lower than those of the remaining five geneticists (i.e., 275,000). George Beadle did not provide an estimate for generation #1 [19].



ED_002751_00030339-00009

Wright and Kauffman meant that the Genetics Panel estimates would only be based on the data from fruit fly and mice [109,110]. Yet, Crow ignored his own imposed 'rules' as he used human data for the upper bound, again without receiving any criticism. This simple vignette of Crow's methodology, its inappropriateness and his violation of his own exclusionary rules and with his actions never being challenged, may explain why the Panel voted not to share their methods and findings with the public and scientific community. Not only would these estimates have been rejected, but their highly acclaimed expert status would soon be challenged and perhaps ridiculed.

The actions of Crow were probably not criticized by other Panel members because significant uncertainties reigned, even by those submitting 'detailed' estimates. For example, in his letter to Weaver on February 20, 1956 [168]; Sturtevant stated

> "After going through these calculations I come out with a feeling that they are rather futile. At almost every step it has been necessary to make a guess, often with little to go on and with no real basis for setting limits within which the true value probably lies."

In effect, Sturtevant was agreeing with the above sentiment of Neel.

These insights of Sturtevant clearly contradict the subsequent more politically correct statement in the *Science* article of the Genetics Panel which asserted that – Each (i.e., expert geneticist on the Panel) thus said, in effect: 'I feel reasonably confident that the true value is greater than my minimum estimate and less than my maximum.' Based on the Sturtevant letter, the statement in *Science* is not true. Even if this statement in *Science* were accurate, it is extremely weak, given the very large range between upper and lower bounds for most estimates.

To make matters even more suspect, consider a further and insightful criticism from Jim Neel, Panel member. He states that the reason for converging of estimates following the elimination of the Demerec, Wright and Kauffman estimates was due to the strategy of Crow to select estimates that were not independent but that used essentially the same assumptions for gene number, mutation rates and other parameters [109,110]. In fact, Neel exposed the bias of Crow's decision to restrict estimates to *Drosophila* and mice, as this would yield the false impression of scientific agreement where there was little or none. Thus, according to Neel[107,108], Crow knowingly biased the assessment in order to create the impression of a high level of Panel expert convergence. This plan fell apart when the Panel had to construct uncertainty estimates (i.e. upper and lower bounds), and an effort to seek a group consensus failed. A similar consideration of Crow's own approach for upper and lower bounds illustrates the unreliability of their estimates.

The continuing duplicity of Crow is displayed in his March 29, 1956 letter to Weaver [39] in which he tells Weaver that 'I suggest one of two things: (a) omit the estimates entirely, or (b) give a single best estimate of the number of mutations, or a narrow range of estimates, based on direct extrapolation from mouse and Drosophila'. Crow then writes 'We then state that these are based on mouse data and let the reader add his own uncertainty factor.'

This letter of Crow illustrates two significant points. The first is that he wanted to opt for showing either no estimates or only a 'narrow range' assuming the convergence of estimates based on mouse and fruit fly data. This suggests that he was trying to ensure that the report would be censored to reflect only the conclusion that he favored.

Secondly, after informing Weaver that he recommended using only the mouse and fruit fly, he states that the reader should be told that the estimates are based only on the mouse. This amounts to flagrant dishonesty. Perhaps he did not want the public to know that predictions for people were based on a fruit fly. He also inexplicably suggested that the reader should construct their own uncertainty factor, using highly censored (i.e., inappropriate) data, lacking upper and lower bounds. This last suggestion reveals that Crow recognized that he and the panel were not able to provide competent expert guidance and that each 'guess' was as good as the next.

Having revealed the internal communications of Crow, Weaver and other Panel members on how they derived genetic risks, it becomes clear that the process employed was scientifically chaotic, inherently flawed, had significant elements of deception and dishonesty, as well as signs of widespread professional incompetence. Yet, while this was being hidden from the public, the process was fully enveloped by an appeal to authority (i.e., U.S. NAS and members who were world leaders and promoted as experts on the topic of radiation induced mutations).

The 100-fold range of uncertainty for the first generation U.S. population mutational responses reported in the *Science* article for the six remaining experts misrepresents data that had already been highly censored. The statement that the uncertainty range for the first generation was based on the six selected expert estimates, as reported in *Science* is not correct, as George Beadle, one of the remaining six, only provided an estimate over 10 generations, not for generation #1. Thus, the article could have stated the uncertainty range of 10–2000 fold for the tenth generation effect (745 mean value) (based on six estimates) and the mean of 756 (100–2857) for the first generation (based on five estimates). Since only five or six estimates were used, an entire listing was very feasible, thereby being fully transparent. However, Crow did not want to show the actual figures or how they were derived as he repeatedly emphasized in letters to Weaver.

The recommendation of the BEAR I Genetics Panel to switch to the LNT for genetic risk assessment was a major event, affecting policy, politics, public perceptions of risk, risk communication strategies, as well as providing scientific foundational support for the efforts of Rachel Carson, in her groundbreaking and highly influential book *Silent Spring* published in 1962.[19] As a result of the publicity generated by the Genetics Panel report the US Congress would hold Congressional Hearings in 1957 on the topic of radiation health risk assessment, with multiple Panel members testifying before Congress in support of the switch to the LNT [66]. The process of getting their message out would achieve a significant and very practical milestone in December 1958 when the US National Committee for Radiation Protection and Measurement (NCRPM) [106] generalized the recommendations of the BEAR I Genetics Panel to include somatic cells, and so by doing, applied the LNT model to the process of cancer risk assessment. Since members of the NCRPM also were members of other high-level advisory committees such as the International Commission on Radiological Protection (ICRP), the adoption of LNT by other advisory groups and regulatory agencies in other countries would follow. The inclusion of the same geneticists on multiple 'independent' Advisory Committees represented a strategy to advance specific policies, giving the LNT supporting committee members more opportunities to promote LNT.

## 7. The BEAR I Genetics Panel in perspective

While LNT became the accepted dose response model for cancer risk assessment as a result of the recommendations of the BEAR I Genetics Panel in 1956, it was readily susceptible to challenges, especially on the grounds that the data were based on fruit flies, not mammals. Making this situation even more potentially contentious was that the BEAR I Genetics Panel voted (i.e., written ballot) not to provide written documentation of the scientific foundations for their decision to recommend the LNT. The reliance upon the fruit fly was rooted in the failed efforts of Donald Charles at the University of Rochester with funding from the AEC during the Manhattan Project to provide findings within a reasonable time period with rodent models concerning ionizing radiation and mutation. Regardless of this striking failure, it was

[19] The historian Ralph [75] states: "not only did she [Carson] tap into this anxiety [about fallout] and direct it toward pesticides, she also used the public's understanding about the hazards of fallout to teach about the similar hazards of chemical poisons."



ED_002751_00030339-00010

generally recognized that the fruit fly model would be an interim one for risk assessment purposes. In fact, this was a principal motivation behind the massive investment on the extensive mouse specific locus test program at the Oak Ridge National Laboratory. Alexander Hollaender, who created and oversaw this initiative, understood that the public health debate would require data from mammalian models just as was provided in other areas of hazard and risk assessment, especially as seen with chemical and pharmaceutical products. With respect to the Genetics Panel not providing a scientific basis for the LNT recommendation, this decision [8,21,54] was passed up the administrative ladder, eventually to the President of the NAS, Dr. Bronk, who did not challenge their decision [9] thereby establishing an inexplicable precedent. The actual underlying explanation was, at least in part, about money, that is, grant money for geneticists. The Panel saw the situation as a type of zero-sum game. That is, if the Panel spent their limited time researching, writing, refining and attempting to obtain agreement on the scientific foundations of their recommendations, then there would be insufficient time to identify funding research priorities for the RF via the actions and leadership of Warren Weaver [9].

Lost in this debate over whether to provide a written scientific justification for the various policy recommendations, including LNT, were the written comments of Muller and his dispute with Demerec and how he could not accept Demerec's bacterial model and his critical judgements of Wright's human genetic damage assessment. Muller would note in a letter about this to the new BEAR Genetics Panel Chairman, George Beadle (see below), 'why should the Panel share its dirty laundry for the world to see?' He had already accepted this fact, stating that 'quarreling geneticists' could not resolve their scientific differences. Based on a copious record of personal correspondence over decades Muller and Crow had a close personal relationship. Consequently, previously undisclosed information as revealed in letters from Muller to Beadle might provide an historical insight as to why Crow excluded the data of Demerec and Wright when assembling the genetic damage estimates of the BEAR I Genetics Panel members as previously noted. The comments of Muller to Beadle permit one to speculate whether Crow's decision to drop Demerec and Wright were initiated by a communication between Muller to Crow. The coincidence seems too great to dismiss the possibility.

The attitude that Muller brought to the issue of providing a technical report to the scientific community that would provide the basis for the Genetics Panel's recommendation is enlightening. He stated to Beadle [97] (now the Chair of the Panel – having just replaced Weaver):

> "As for the preparation of a technical report ..., it seems to me that it would involve us in a lot of thankless work and disputatious rehash of points we have already considered, as well as airing our dirty linen before the public unnecessarily."

Muller then goes on to state:

> "After all, only geneticists would be competent to judge the validity of our technical report and geneticists do not need it...."

Of particular importance were his follow up comments:

> "So far as I can see, it would be a matter of quarrelling over what would be the most important points to put in and to what extent they were valid, things on which I thought we had agreed to disagree. Why, for instance, should I enter into a public dispute with Demerec on whether a bacterial generation[20] should be taken as corresponding just as closely to a human generation as a Drosophila generation does? This is only one little example of many ... ... Similarly, I think I would have to disagree with Wright concerning the frequency and importance of small detrimental mutations as contrasted with the conspicuous ones known as lethals and visibles."

This correspondence of Beadle and Muller may therefore provide pivotal insight into the dynamics of the Panel, their need for grant funding, why they failed in their responsibility to the country, and how Muller sought to blunt the influence of Demerec and Wright in the internal Panel disputes. It also revealed how Weaver and Crow were willing to disrespect one person's area of expertise, even after it was stated that it was their goal to integrate and assess the estimates of each expert from the diverse fields within genetics.

## 8. Dose-rate: Russell's challenge to LNT

While December 1958 would prove to be significant for the adoption of LNT for cancer risk assessment based on the actions of the NCRPM, it would also be ironically important for a potentially significant challenge to the scientific foundations of LNT. This challenge would become evident on December 19, 1958 when the journal *Science* published a significant paper by William L. Russell and colleagues [141] from the Oakridge National Laboratories demonstrating the effect of dose-rate for ionizing radiation-induced mutation in spermatogonia and oocytes in the mouse model. The findings of Russell were broadly significant enough to become a front-page story in the *Buffalo Evening News* as written by the Pulitzer Prize Winner Nate Finney [49], who had a long and serious interest in the societal and public health implications of atomic energy and nuclear weapons. The first public sensing of Russell's work was revealed four months earlier in an August 16, 1958 story in the *New York Times* [142]. However, at the time of the *Science* publication in December 1958 the *New York Times* was on strike, leaving the reporting field wide open for the *Buffalo Evening News* reporter [138].

The Russell findings were significant because over time they would unequivocally refute the LNT mantra of the radiation genetics community. These mammalian findings with spermatogonia and oocytes would indicate that radiation-induced mutation damage was not cumulative and could be reversible and the dose response therefore should not be assumed to be linear. The findings also suggested to Russell that DNA-repair must occur even though it had not yet been discovered.[21] In fact, Russell's (and Altenburg's) inferences were correct. The Russell data were seen as a possible game changer and would quickly affect research directions for the field. It was indeed ironic that within a week or two of the accepting of LNT by the NCRPM, its possible demise was being featured in the most prestigious scientific journal in the world.

Analyses of the Russell scientific writings and correspondence reveals that he tried hard not to explicitly and directly challenge the radiation geneticist community and the seemingly exquisite sensitivities of Muller. Russell was performing a type of balancing act, that is, he was trying to promote his findings while adhering to the radiation geneticist mantra and still supporting the LNT. As can be seen from the published literature and correspondence (Russell letters/memos to Muller [133–135], Muller letter to Russel [98], Russell would maintain this (and perhaps torturous) position until Muller's death in April 1967 when he would finally and unashamedly confront the radiation geneticist mantra on each of its fundamental tenets with the mammalian data he had accumulated over more than two decades on dose-rate

[20] It should be noted that Demerec had an extensive publication record with *Drosophila*, spanning two decades and more than 50 papers in the peer-reviewed literature. He also had a strong publication record with bacterial mutations. Thus, Demerec was uniquely qualified to see the relationship of bacterial susceptibility with that of *Drosophila*. In fact, he was far more experienced in this than Muller. Furthermore, Demerec was originally trained as a maize geneticist with Emerson at Cornell for his Ph.D. in the most prestigious group in the U.S.

(*footnote continued*)
Demerec was perhaps the most broadly experienced geneticist in the country.

[21] Edgar Altenburg would write Muller about the novel Russell findings, likewise suggesting the existence of DNA repair (Altenburg to Muller, December 27 [2]).



ED_002751_00030339-00011

[137]. More immediate, however, was the fact that within a few months after the publication of the Russell findings, Muller had shifted over his lab to now incorporate dose-rate studies with *Drosophila* based on the research methodology of Russell [24,25]. This represented a significant shift as Muller's earlier research on dose-rate with Ray-Chaudhuri [131,132] involved only mature fruit fly spermatozoa. With the switch to the use of earlier stages of reproductive cells, Muller was reporting that he, too, now had observed the dose-rate phenomenon [119].

The findings of the Russell and Muller dose-rate research found their convergence in the report of the next BEAR Genetics Panel (i.e., BEAR II) chaired by George Beadle, Nobel Prize recipient (1958) in its 1960 publication ([103] – BEAR II). The incorporation of this information came late in the Panel process and probably would not have happened without a last minute intercession by Russell and his director at Oak Ridge, Alexander Hollaender, who requested/challenged George Beadle to ensure that the dose-rate information be included. Beadle agreed and instructed Russell and Hollaender to write that section of the report [64]. The re-written report was then sent to all members of the Panel, including Muller, with a summary of the preliminary fruit fly dose response data of Muller. However, unlike the BEAR I Genetics report, the BEAR II Genetics Panel Report (1960) was not widely distributed, had little to no acclaim and no ostensible impact on the field or public policy based upon citation, follow up debate, and other possible spin-off activities. Nonetheless, the BEAR II Genetics Panel acknowledged the existence of dose-rate in their 1960 report in both mice and fruit flies. However, while the Genetics Panel finally recognized the biological reality of dose-rate, they failed to confront the issue of the generalization of the 1958 NCRPM LNT recommendation to somatic cells. The new dose-rate findings were a potentially significant scientific problem that could discredit the major dose response policy recommendation to support LNT.

Within a few years, it would become clear that a possible explanation for why the dose-rate phenomenon might not have been observed in the earlier Ray-Chaudhuri study (1939, 1944) was because the mature spermatozoa lacked the capacity for DNA repair while this capacity was present in somatic cells and spermatogonia and oocytes. Thus, reliance on mature spermatozoa, which lack the capability of DNA repair, as the basis for cancer risk assessment using the LNT model was/is a fundamentally flawed approach. Yet, it was within this framework that LNT was created and 'matured' into broad acceptance within the scientific and regulatory worlds of the 1950s and 1960s as guided by Muller and the radiation genetics community.

The 1960s revealed that Russell's research would be extended so that it enabled a clear threshold response to be observed for mouse oocytes at a 'relatively' low dose-rate. The oocytes displayed a threshold for genetic damage at an exposure rate that was 27,000 times above normal exposure to radiation in the U.S. from background and other exposures [136].

The data of Russell created an important rift within the radiation genetics community. This was highlighted by an article of Harold Plough [129], a professor of biology at Amherst College, and former genetics graduate student with Muller at Columbia. Plough was also the person who helped to facilitate a position (i.e., Amherst College, 1940–1945) for Muller in the U.S. upon his return after an eight-year hiatus and with no other available offers. This rift was significant as Muller and another (future) Nobel Prize recipient Salvador Luria, excoriated Plough as seen in letter exchanges and in articles/letters-to-the-editors to the *Boston Globe* (Menzies, June 19, [83]); Luria, July 2, [74]; page 18) and *Washington Post* (Simons, June 19, [147]). During this dispute, Jim Crow wrote to Muller, telling him that Plough was totally out of step with the rest of the radiation genetics community and that no one believed that thresholds for radiation-induced mutation exist [40]. The letter of Crow was curious since it was written after the BEAR II Genetics Panel (1960) (of which he and Muller were members) acknowledged the findings on dose-rate for Russell and Muller and after reports of Russell which clearly showed that a threshold exists for the mouse oocyte for ionizing radiation induced mutation. The letter of Crow to Muller was never challenged or corrected by Muller, despite its obvious factual flaws.

During the same time interval, Muller would become engaged in a substantial debate over the role of dose-rate in human risk assessment especially within the context of his role on expert committees of the ICRP [23–25]. In these debates, he claimed that the dose-rate data were inadequate to apply to human risk assessment. Part of his rationale was that differences in dose-rate responses between insects and mammals had not been resolved and therefore the mammalian data of Russell should not be used in human risk assessment. Yet, he argued that there was an evolutionary basis for this apparent interspecies difference in which dose-rate would have been more strongly selected for in mammals than in insects [99]. The point here is that at every possible turn Muller would attempt to preserve LNT, even if it meant being deceptive and dishonest (e.g., his comments about Caspari's control group) or inconsistent, as in this case, or imposing of censorship as in the case of his dispute with Demerec [48] and in his attempt to prevent Neel from speaking at an international symposium on his Japanese atom bomb survivor data ([25]; footnote 1).

## 9. Russell challenges radiation genetics mantra

While Russell finally broke ranks with the radiation geneticist community, it was not until the 1969–1970 time period as revealed in several publications and conference presentations (Table 4) [136]. In his 1970 presentation at the 14th International Congress of Radiation Research at Evian, France, Russell [137] stated that the original estimates of genetic risk (which were made by the BEAR I Genetics Panel) [7] for radiation (and, as noted by Ref. [17]) and later for chemical carcinogens were based on the two major assumptions that: (1) radiation-induced gene mutation frequencies in the fruit fly have extrapolative relevance to humans and (2) results from radiation experiments on fruit fly spermatozoa illustrate general principles of radiation genetics and thus can be applied to humans (i.e., the mantra of the radiation geneticist). What followed from these two overreaching assumptions was a series of six specific and fundamental risk assessment tenets (i.e., "general principles") upon which genetic and, as noted by Calabrese [17], cancer risk assessments were based. According to Russell [137], his radiation geneticist colleagues believed that,

> 1) Gene mutation rate is directly proportional to radiation dose; 2) Gene mutation rate is independent of radiation dose rate; 3) Gene mutation rate is independent of dose fractionation; 4) There is no repair of gene mutational damage; 5) There is no threshold below which no genetic damage occurs; and 6) There is no recovery from mutation with time after irradiation.

Following two decades of conducting genetics research on mice at Oak Ridge National Laboratory, Russell had evaluated the effects of ionizing radiation on over a million mice (radiation-exposed and control groups combined) in the largest progressive/cumulative mammalian study ever conducted. From this extensive experience, Russell [137] concluded that, ' … the first assumption is probably not valid, that the second is definitely incorrect, and that none of the six 'general' principles applied to mouse spermatogonia and/or oocytes.' During his presentation, Russell offered scientific evidence supporting these conclusions. This presentation had the potential to be a major galvanizing event that led to substantial debate while offering the opportunity for a significant mid-course correction concerning the nature of the dose response in the low dose/dose-rate zone. However, it failed to do so.

During this period (i.e., 1970) Russell would accept membership on the first NAS BEIR Genetics Subcommittee (BEIR I) which was to be chaired by Jim Crow. The central issue of this Genetics Subcommittee would be how it would address the nature of the dose response in the low dose zone. In effect, this was to be the next battle in the threshold versus LNT confrontation. It was then about 15 years since the



ED_002751_00030339-00012

precedent-setting BEAR I Genetics Panel report of 1956. During that time, the environmental revolution had started in earnest following Carson's [30] book, *Silent Spring*, the passage of the National Environmental Protection Act (NEPA) following the massive Santa Barbara oil spill in January/February 1969, signed into law by the U.S. Congress in December 1969, and the creation of EPA in 1970. Likewise, the role of quantitative risk assessment using low dose modeling received a strong boost by the seminal publication of Mantel and Bryan [76] that introduced the concept of low dose modeling for cancer risk assessment. This publication originated from the herbicide (i.e., aminotriazole) Cranberry scare during Thanksgiving of 1959 in the U.S. during the Presidential campaign between John F. Kennedy and Richard M. Nixon [65].

Mantel and Bryan [76] proposed that an arbitrary acceptable risk for carcinogens be set at 1/100,000,000 ($1 \times 10^{-8}$) over a lifetime using the probit model. Regardless of the model, the concept of acceptable risk rather than reliance on a true biological threshold had taken hold at the National Cancer Institute (NCI) for chemical carcinogens and at the NAS for ionizing radiation. The creation of the BEIR I Genetics Subcommittee in 1970 occurred at a strategic moment as it was at the time of EPA creation, yet, before the Agency had constructed guiding principles for carcinogen regulation in the mid-1970s. Thus, even though the NAS BEIR I Committee was created to offer guidance to the country on the health concerns associated with the expansion of the domestic use of ionizing radiation, its recommendations would be more broadly influential, serving as an ideal source of highly respected scientific/public health guidance for environmental cancer risk assessment.

## 10. BEIR I

Following the death of Muller on April 5, 1967, the BEIR I Genetics Subcommittee (1970–1972) addressed the question of cancer risk assessment anew. They did this by reviewing what the BEAR I Genetics Panel wrote some 15 years before and reflecting upon what had been learned in the interim years. While much was discussed, several key concepts and findings emerged. The most important conclusion of the BEIR I Genetics Subcommittee was that the BEAR I Genetics Panel of 1956 made a mistake on the key concept of dose-rate. This conclusion was based on the data of Russell from the mouse specific locus test, which subsequently had matured and expanded, now having more than a decade of widespread exposure and scrutiny within the scientific community. Being wrong on dose rate was not a simple or singular point. It meant that genetic damage was not cumulative, could be reversed, and was repairable. These findings exposed multiple flaws in radiation geneticists' central beliefs. In the period between the discoveries of Russell in 1958, to the creation of the BEIR I Committee in 1970 DNA repair had been discovered, as predicted by Russell. The basis for the recommendation of LNT had, therefore, been convincingly challenged on scientific grounds.

The BEIR I Genetics Subcommittee also raised another fundamental point that challenged the BEAR I Genetics Panel report. This concerned the fact that the LNT, as derived from fruit fly data via the research of Muller and Ray-Chaudhuri and the Stern-Manhattan Project studies, used mature spermatozoa that were now known to lack DNA repair. The use of a biological model lacking DNA repair to estimate risks in somatic cells possessing DNA repair is fundamentally inappropriate. Yet, that is precisely what the LNT-based cancer risk assessment paradigm had long been based on. BEIR I also knew that it had to transition to the so-called modern era-that is, adopting a rodent model with cells that possessed DNA repair. The real challenge was whether they could do this and still retain LNT. This was an especially significant challenge since the dominant intellectual and ideological paradigm amongst the geneticists was LNT, a perspective that had become rooted not only in the science, but also within their culture.

In contrast to the BEAR I Genetics Panel, the BEIR I Genetics Subcommittee provided a written basis for their recommendation of the adoption of the LNT. This recommendation was very much like a reaffirmation of the status quo, lacking the fairness of an independent competition between two ideas (i.e., LNT vs threshold). In the case of the threshold vs LNT debate the Genetics Subcommittee would not only play a significant role but so to would the findings from animal studies and epidemiology.

These two disciplines represent important components in the overall risk assessment process. However, neither of these complementary methodologies is capable of adequately addressing the LNT question. This can be best appreciated by the fact that the mega-mouse study of the U.S. FDA, which used over 24,000 mice could only confidently estimate risk down to the $10^{-2}$ (1/100) area and is therefore referred as the ED01 study [11]. The limitations of epidemiology are also widely known within the legal system in the U.S. only accepted as a causal judgement when the odds ratio is ≥ 2, that is, when the risk at least doubles [164]. This is far greater than values of $1/10^6$ (or even 1/10) that are implicit in present risk assessment practice.

The BEIR I Genetics Subcommittee based their judgement in large part upon a belief in the mechanisms of radiation induced cancer, and this was due to an initial event that involved mutagenicity, a view now widely seen as insufficient, requiring multiple steps/stages [48].[22]

If it could be shown that the dose response for mutagenicity was linear at low doses, it was widely believed that the dose response for radiation-induced cancer would also be linear. This was precisely why the mantra of the radiation genetics community of cumulative, irreversible and linear was central to the risk assessment process and regulatory Agency policy. The challenge facing the BEIR I Genetics Subcommittee was that now the paradigm-changing data of Russell had taken center stage. Russell's data was not trivial but based on the findings of more than a million mice in the largest cumulative mammalian genetic toxicity program ever undertaken. It was an example of Big Science and was funded and located within the AEC, which later became the ERDA and later still the Department of Energy. As such, it was a program that involved a large number of professional staff over several decades. The government had made a massive investment in this area for the explicit purpose of having a solid scientific foundation for the risk assessment process for ionizing radiation.

Over the decades since the 1950s Russell and his team published numerous papers on their progressive studies, with accumulating sample size. The initial striking findings of the 1958 *Science* journal paper, which demonstrated the existence of dose rate effects in spermatogonia and oocytes were confirmed and strengthened with its massive cumulative size. The findings for the male indicated that by lowering the dose-rate the mutation damage incidence could be significantly reduced as compared to the same total dose given acutely. The research demonstrated that the mutation incidence could be reduced by about 70% in males. In a series of parallel experiments with females, they demonstrated that at 'low' dose-rates that the amount of genetic damage could be reduced by 100%, that is, the low dose-rate females became indistinguishable from the controls. The findings of Russell were of striking significance, especially for the females since they demonstrated the unequivocal existence of a threshold for genomic mutation as induced by ionizing radiation. The mechanisms by which these decreases in mutation rate occurred was explained by the presence of DNA repair. Why the male did not return to the control group value as did the female was not known at that time. While it would seem that answering the question of why the females achieved a

[22] The actions of the BEIR I Genetics Subcommittee were deeply rooted in the Somatic mutation theory (SMT), a view that has directed cancer risk assessment to the present. While not the focus of the present paper, the SMT has been challenged from multiple perspectives [134,151,152] over the past decade. How such developments may affect the federal cancer risk assessment criteria remains to be seen.



ED_002751_00030339-00013

threshold and the male did not was extremely important, it was never resolved by the BEIR Genetics Subcommittee. A possible technical reason why it could not be easily addressed was because the number of exposure days was limited by the duration of spermatogonial development. This placed a constraint on what dose/dose-rate could be delivered to a particular stage of cell development, essentially limiting research to resolve the male threshold issue.

When the BEIR I Genetics Subcommittee [105] evaluated the Russell data it acknowledged the existence of dose-rate and the threshold response of the female. It also noted that the male spermatozoa showed a decrease by 70% in mutation rate as compared to the acute exposure, but still not a threshold. Based on their report, there was no discussion of why, from an evolutionary perspective, the oocytes would display a threshold while the spermatogonia did not. For example, perhaps the spermatogonia were simply progressively lessening their DNA repair capacity that would eventually result in the DNA repair deficient mature spermatozoa. Alternatively, perhaps a threshold may have been detected had lower dose-rates been evaluated. Is there an evolutionary reason why such a gender-difference would exist? Would such a difference exist in somatic cells? Of course, these questions were all premised on the assumption that the Russell findings were correct, accurately presented and interpreted. The judgement of the BEIR I Genetics Subcommittee was that the LNT should be retained/adopted based upon the spermatogonia of the Russell data. They decided to construct a linear dose response from the lowest dose tested (i.e., dose associated with the ~70% decrease in mutations in males) to the origin. They also made the assumption that the spermatogonial cells would be a better representation of somatic cells than mature spermatozoa. Thus, the BEIR I Genetics Subcommittee transitioned from dependence on the mature spermatozoa of the fruit fly for the LNT recommendation to the Russell findings with mouse spermatogonia while still retaining the LNT.

The BEIR I Genetics Subcommittee report [105] proved to be highly influential as it would serve as the basis for how U.S. regulatory agencies would estimate risk for both ionizing radiation and chemical carcinogens. This was first reported in 1975 (and reaffirmed two years later in 1977) by the US EPA. The agency explicitly cited the Genetics Subcommittee report and the dose-rate findings of Russell as described in the following quote from Calabrese, 2017b [25]-see quote, page 456):

> "EPA uses primarily the recommendations of the National Academy of Sciences Committee on the Biological Effects of Ionizing Radiation (BEIR) as expressed in the November 1972 report to arrive at dose to health conversion factors. Besides the concept of linearity expressed in the policy statement (i.e., EPA, 1975– EPA Policy Statement on Relationship between radiation dose and effect. 41 Federal Register, 28409), it is further assumed that health effects that have been observed at dose rates much greater than those represented in this report are indicative of radiation effects at lower dose rates. Any difference in biological recovery from precarcinogenic radiation damage due to low dose rates is neglected in the BEIR health estimates."

The U.S. EPA Carcinogen Assessment Group (CAG) under the direction of Roy Albert [1] would also explicitly cite the recommendations and rationale of the BEIR I Genetics Subcommittee (1972) [105] as providing the basis for the use of LNT for the assessment of risk for chemical carcinogens. The EPA accepted the LNT model of the AEC/BEAR I Genetics Panel. This model was adopted by EPA since it was easy to apply. From a toxicological perspective, the agency simply had to identify the lowest dose of carcinogen that induced a statistically significant response and then draw a straight line to the origin of the graph in order to estimate cancer incidence at any exposure level. The biological plausibility of the LNT model was based on the assumed linearity of mutation dose response as recommended by BEAR I and BEIR I, within the framework of target theory. Albert [1] indicated that ' … any difference between chemical carcinogens and ionizing radiation could be waived aside as they both cause genetic damage … '. Thus, in retrospect, the long term investment in the research by Russell on the mouse specific locus test, which started in 1949 at Oak Ridge National Laboratory, proved to be a highly successful endeavor as it now provided the scientific rationale for carcinogen risk assessment for all U.S. regulatory and public health agencies.

The Russell findings were so massive and credible that they served as the fundamental basis for understanding how ionizing radiation and genotoxic carcinogens would act at low doses/dose-rates. This became a type of toxicological 'homing device' that complemented the necessary (and significant) but insufficient whole animal and epidemiological data which lacked the power to confidently assess low dose/ambient exposure effects. In effect, the Russell findings became the gold standard, providing the intellectual rationale for linearizing carcinogen dose responses. Despite this reaffirmation of the LNT, it was insufficiently appreciated that this foundation, based on the Russell data, had its own significant inconsistencies. For example, the oocyte showed convincing evidence of a threshold even at doses about 27,000 fold greater than background. There was also no data to indicate that the male, even though not showing a threshold at doses comparably greater than background, might not show one at lower doses/dose-rates. Nonetheless, this was the basis of the LNT over the next half century. Over this period of time many thousands of new research papers were used by proponents and opponents of the LNT but the rationale for the LNT would remain the same. It would revert back to BEIR I, the Genetics Subcommittee and the Russell findings. Even multiple studies showing that cosmic/terrestrial ionizing radiation appears necessary for improving a wide range of health indices in multiple species [51,67,128] was not sufficient to make a change from LNT.

## 11. BEIR I error discovered and corrected

Nearly 25 years (in 1995) after the convening of the BEIR I Genetics Subcommittee, Paul B. Selby, a senior geneticist at Oak Ridge National Labs, and a former Ph.D. student of William L. Russell, uncovered significant irregularities in the construction of the historical control group used in all the major mouse specific locus test studies and risk assessment applications. The irregularities were of such potential magnitude as to warrant an external assessment by a committee of four leaders in the field. The external expert committee, plus the Russells' and Selby agreed that the control group required correction, with an adjustment upwards for mutational incidence. The Committee requested the Russells and Selby publish their adjustments in the scientific literature. The Russells adjusted the mutational rate upwards of 120% [140] while Selby argued that the control values were wrong by 5–7 fold [144]. While this dispute was contentious, the tone of these published articles was non-inflammatory making it difficult for the field to appreciate the seriousness of the debate and its widespread implications. Over time, publications accumulated which addressed many of the issues debated by the Russells and Selby [140,144,145]. The net result was that the arguments of Selby had grown in statue with broad acceptance by leading radiation geneticists [24,25].

Despite this ongoing process, it was only recently that the question was raised concerning how would the Russell and Selby adjustments have affected the judgements/conclusions of the BEIR I Genetics Subcommittee [23–25]. This was a relevant question, for if the Russells had provided accurate control group information, it would have been available for the BEIR I Genetics Subcommittee through their 1970–1972 meeting period. In a recent paper, it was shown that if the Russells' upward correction had been made at the time of the BEIR I, the data would have revealed that the male mutation incidence at the low dose-rate would have displayed a threshold (i.e. the 70% decrease in mutation would be 100% with the error correction) [24,25]. If this had been the case, then the argument used by the BEIR I Genetics Subcommittee for the adoption of the LNT would have been invalid.



ED_002751_00030339-00014

Furthermore, if the analysis of Selby had been available and used, it would have supported a possible hormetic dose response interpretation.

These new findings are significant, since they argue that the basis of the modern LNT as originated with recommendations of BEIR I, was based upon a mistake and are therefore invalid. While science is supposed to be self-correcting, it is clear that it has taken nearly half a century for this error to be recognized and a correction proposed. The reasons for such a prolonged failure to detect the control group error are likely many, but require speculation. Perhaps the most reasonable is that the mouse SLT was a unique bioassay, requiring massive resources. It could only be conducted in large governmental laboratories. There was only one such location in the U.S. This would become an issue because many technical questions and methodologies were unique to the specific locus test, limiting the number of people with adequate expertise to review and correct possible errors. It also exposed flaws in the peer-review process. Journal editors may have been at a loss as to whom to send the Russell manuscripts to. This leads to an appeal to authority and an unwillingness to challenge authorities such as Russell. In fact, the only challenge would originate internally, which is not a surprise, as very few would have known as much as Selby and to have been in a position to offer highly technical criticisms.

Such corrections, when applied to the risk assessment actions of BEIR I, indicate that those actions would also need to be adjusted. This adjustment would confront the issue of whether this central and dominating recommendation of BEIR I that lead to the reaffirmation of LNT should be changed. In retrospect, the data indicate that the NAS BEIR I Genetics Subcommittee used the Russell data to re-affirm the LNT model and did so not knowing that the historical control data used in the Russell publications was incorrect by from 2 to 7 fold. Given the prestige of the NAS, the complexity of the mouse SLT, and the high esteem of the Russells, the data and the recommendation were assumed to be accurate. This unprecedented situation created the perfect scientific storm: the entire carcinogen risk assessment process of the US and essentially all other countries with appropriate regulatory governmental structures was based on a significant undetected mistake that is still guiding cancer risk assessment today.

## 12. Discussion

The history of the LNT is shown to have originated as an attempt to discover a biological mechanism that could explain evolution. While this proposal of Olson and Lewis [118] failed to be convincing, their idea that the dose response for radiation-induced mutation should follow a dose-related direct proportional relationship (i.e., a linear dose-response) was persuasive, at least to the radiation geneticist community. This view was quickly adopted by Muller and supported by laboratory findings under his direction. Muller would soon become the dominant influence in formulating the proportional response concept, its generality and scientific implications (i.e., Proportionality Rule). Soon after these descriptive developments of the Proportionality Rule model, the next step was the development of a proposed mechanism. This was achieved in 1935 by Timofeeff-Ressovsky et al. [169] in their classic paper that has been rediscovered, translated, and given modern prominence [150]. This action added the concept of target theory by leading physicists to provide the mechanism. Complementing the mechanism, Zimmer [180], one of three authors of the key 1935 [169] paper, provided the mathematical formulation, which functionally showed that the LNT model was due to a single hit (Fig. 1). It was this sequence of actions, which were the fundamental scientific building blocks of the modern LNT-single-hit model. Muller would then secure the biological credibility of the LNT in subsequent studies with Ray-Chaudhuri [131,132]; which indicated no support for the dose-rate concept. Total dose was all that counted, regardless of whether ionizing radiation was given acutely or chronically. This perspective would translate into a linear dose response model with adverse effects being predicted down to a single ionization. While Muller strongly supported the LNT, it is important to note that highly credible data challenging the LNT judgement were generally ignored or marginalized, even though having scientific credibility (Table 1).

The radiation genetics community was intellectually led by Muller, even though there were many strong personalities within the group. Muller was unique amongst the other talented radiation geneticists, showing a very strong commitment, extremely attentive to detail, with a highly critical and combative demeanor. As a result of his leadership, the field adopted his view that radiation induces mutation in a linear fashion. This group of radiation geneticists wanted this view to guide medical treatments and health/exposure standards for the general public and workers.

The entire scenario just described was based on the incorrect interpretation by Muller of X-ray induced gene mutation in *Drosophila* at very high doses and how this error mesmerized the scientific community and government leaders even in the presence of credible and devastating criticism by Stadler and others. Thus, the LNT-SH model was based on a mistake and consequently led to the flawed cancer risk assessment recommendations of the NAS BEAR I (1956) [9] and BEIR I (1972) [105] expert panels. Muller was therefore able to mislead the field, regulatory agencies and even the Nobel Prize committee. In fact, despite having been shown to be incorrect on his interpretation that he induced gene mutation, his views still control the textbooks and governmental risk assessment policies worldwide, even in 2019, despite overwhelming modern data to the contrary.

From my perspective, the initial two decades of LNT development occurred in a manner that was typical of novel concept challenges and acceptance within science and society. This process became problematic and controversial only after Ernst Caspari, in August 1946, presented his data to Stern. These data did not support the Muller-Ray Chaudhuri lack of dose-rate findings. When seen in the perspective established above, one can better appreciate why Stern rejected the contrary findings of Caspari and why Demerec [3] was so concerned that he implored Caspari with the statement, 'What can we do to save the hit theory.' Stern and Muller, key leaders of the radiation genetics community, were strikingly challenged by the new data. The Manhattan Project was far more advanced than the research of Ray-Chaudhuri with Caspari's study having improved quality control and study design features. Earlier papers (e.g. [15]), revealed a series of

**Table 4**
Summary of the effects of dose-rate on the induction of mutations by radiation in the mouse (Source: [136]; page 623)*.

| Russell Quote: |
|---|
| "Using the genetic techniques available today and the data discussed above, it is of interest to estimate the frequency of mutations that would be expected if a population of mice received the maximum gonadal dose of radiation (5 rem over a 30 year period) allowable for the general population in addition to background radiation. This radiation dose of 5 rem would be received at a dose rate of approximately $3.3 \times 10^{-7}$ r/minute (0.00000033r/min). This is a dose rate that is over 27,000 times smaller than the lowest dose-rate used in studies with female mice in which no induced genetic effect was observed even when a dose of 400r was used. Therefore, no significant effect would be expected from this low dose (5 rem) even if it were delivered at a considerable higher dose-rate. This dose-rate is also 3000 times smaller than the lowest rate used in experiments with male mice. The lack of a threshold dose-rate, however, when males are considered means that one would expect mutations to be induced at the seven specific loci, and these could be detected, but an extremely large and costly experiment would be necessary. For example, if one uses the mutation rate obtained in the low dose-rate experiments, $8 \times 10^{-8}$ mutations/locus/gamete/r, one would expect 280 mutations/100 million gametes or progeny tested ($8 \times 10^{-8}$ mutations/locus/gamete/r) (7 loci/gamete) (5 rem). This, obviously, is an experiment which is not feasible to carry out from any standpoint." |

*Even this assessment by Russell is now recognized to have significantly overstated the mutation risk due to an error in the historical control group. Correction of this error using the Russell adjustment reveals a threshold response. Correction of this error using the Selby adjustment suggests an hormetic response [24,25].



ED_002751_00030339-00015

irregularities in judgements and behavior by Stern and Muller, first occurring after Caspari presented his data to Stern. These include:

1. Stern directing the writing of the manuscript discussion that challenged the acceptance of the Caspari data.
2. Writing a discussion that placed greater credibility on the acute exposure Spencer experiment that had numerous limitations. The support for the Spencer data was due to its apparent demonstration of a linear dose response (i.e., supported the geneticist mantra) – not to its scientific quality.
3. Muller's disavowing the possibility of a threshold at his Nobel Prize lecture, even after he had seen the Caspari data supporting a threshold and had strongly recommended that funds be obtained to replicate it.
4. Both Stern and Muller promoting the validity of the Delta Uphoff experiments which had aberrantly low control group values, which Uphoff and Stern stated in writing made these data uninterpretable.
5. Uphoff and Stern publishing a note in *Science* that included the uninterpretable findings and not sharing with the readership why data, unacceptable less than a year before in the formal report to the AEC, were now acceptable.
6. The failure of Uphoff and Stern to fulfill their pledge to the *Science* readership that they would publish a follow up paper with detailed methods, materials and supportive data.
7. The false reporting by Muller [94,95] that Caspari had an aberrantly high control group value, while his own data and memos explicitly confirmed the findings of Caspari and discredited the control data of Uphoff.

These obfuscations and deceptions by Stern and Muller would not only enhance the acceptance of the Uphoff and Stern [172] paper but would also lead to marginalization of the Caspari findings [148,149]. The goal of the Stern and Muller actions was no less than that of Demerec, which was to save the LNT SH model and to promote its acceptance. The perspectives of Stern, Muller, and others in the radiation genetics community were also shared by the leadership of the Rockefeller Foundation who selected geneticists who were LNT advocates for the NAS BEAR Genetics Panel. This bias was also seen in the selection of Weaver to Chair the Panel and his inappropriate remarks that (1) raised the possibility of sizable and highly flexible grant money for geneticists if their report was 'appropriate', (2) the inappropriate actions of Crow to exclude three technical estimates of genetic damage by the contributing geneticists, (3) the false reporting in *Science* by the BEAR I Genetics Panel concerning the number of panel members who provided radiation risk estimations, (4) the misrepresentation of variability of the six (i.e., five) estimates of the Panel and (5) the actions of the President of the NAS to support a decision of the BEAR I Genetics Panel not to provide a written report explaining the scientific basis of their recommendations.

Led principally by Muller, the BEAR I Genetics Panel was successful in convincing essentially all major advisory groups and countries to adopt their LNT recommendation. This scientific saga would be renewed with the dose-rate findings of Russell in the mouse model. Even though the findings of Russell would essentially disprove the radiation genetics core concepts of cumulative, irreversible and linear responses, the BEIR I Genetics Subcommittee, some 15 years after BEAR I, could not break free from the hold on the field that Muller had imposed and passed on to his scientist protégées, such as Jim Crow, who chaired the BEIR I Genetics Subcommittee. Finally, due to the vigilance and courage of Paul B. Selby [144,145,], key mistakes by Russell were revealed, forcing a revision of the Russell dose-response findings in 2017 [24,25], leading to a highly credible challenge to the LNT model.

Not to be forgotten in the LNT story is Muller's Nobel Prize. The international prestige of the Nobel Prize, received by Muller in 1946, provided enormous and enduring support for Muller's career, the field of radiation genetics, and the LNT. The awarding of the Nobel Prize for the production of x-ray-induced gene mutations provided the necessary credibility for the transformation of a clearly flawed hypothesis into a major environmental and public health belief system and cancer risk assessment policy. The Nobel Prize Committee's decision transformed a progressively discredited hypothesis (in light of the research of Stadler, McClintock and others) into a biological 'truth' following health concerns generated by the dropping of the atomic bomb in 1945 in Japan. The widespread adoption of the LNT may be directly tied to a flawed decision by the Committee to award Muller the Nobel Prize. It is likely that without the 'boost' provided by the Nobel Prize for Muller the history and acceptance of LNT would have been significantly affected.

The history of the LNT is complex, strikingly revealing the intersections of science, personalities, politics, power, financial temptations, and most importantly, beliefs. While a substantial part of this story was pieced together from the peer-review literature, other findings and insights were revealed via the NAS meeting transcripts and numerous letters, memos, and preserved papers of members of the NAS Genetics Panels and others. In fact, unless strenuous efforts were made to obtain and explore these additional sources of information, the story of LNT would still remain obscured and a false representation would persist regarding what the historical record now reveals.

## 13. Conclusions

The LNT single-hit dose-response model for cancer risk assessment was conceived, formulated, and applied in a manner which is now known to have been scientifically invalid. Contributing to the embrace of the LNT model were a series of scientific errors and the unfounded assumption that one could accurately extrapolate potential risk from very high to very low doses of ionizing radiation. This occurred despite findings indicating that (1) the type of genetic damage/mutation spectra is highly dose dependent (i.e., mostly gene deletions at the high doses used by Muller and not gene mutations), precluding accurate and valid low dose extrapolation, (2) the use of mature *Drosophila* spermatozoa which are haploid and lacking of DNA repair to extrapolate to mammalian somatic cells which are diploid and possess efficient DNA repair, and (3) the rejection of dose-rate in risk assessment which is now an important concept in ionizing radiation risk assessment. Thus, the concept of LNT single-hit for cancer risk assessment is shown to have multiple flaws that reveal its lack of scientific validity. However, despite these flaws the radiation genetics community of the 1940s-1960s promoted and strongly advocated the adoption of the LNT single-hit model to replace the threshold model. As documented in this review, on numerous occasions leading members of the radiation genetics community abandoned their scientific role and instead became ideological advocates for the LNT single-hit model, displaying questionable judgements and behaviors that reflected efforts to obfuscate, deceive, and even misrepresent the scientific record. These actions clearly played a significant role in the successful adoption of the LNT by the scientific and regulatory communities, as well as in widespread public health policy. By the early 1970s numerous limitations of the BEAR I Genetics Panel cancer risk assessment approach were recognized by the BEIR I Genetics Subcommittee, by replacing the fruit fly with a mammalian model and using diploid cells with DNA repair showing clear dose-rate effects. Nevertheless, LNT was still retained since a threshold for mutagenicity was only found in oocytes, and not in spermatogonia. However, more recent re-evaluations of the scientific basis of the BEIR I Genetics Subcommittee show that the data upon which its judgement was based were in error, requiring a significant historical control group adjustment. These adjustments now unequivocally reveal that the responses of both male and females displayed threshold dose responses, indicating that the basis of cancer risk assessment as recommended by the NAS BEIR I Subcommittee and accepted by virtually all regulatory agencies, is demonstrateably incorrect. These new findings have profound implications for regulatory agency cancer risk assessment, cost-benefit analyses, numerous public health practices, technological



ED_002751_00030339-00016

developments, use of nuclear power, and risk communication messages to the general public for both radiation and chemicals.

## Declaration of interest

Author declares no potential conflict of interest.

## Acknowledgments

EJC acknowledges longtime support from the U.S. Air Force (AFOSR FA9550-13-1-0047) and ExxonMobil Foundation (S18200000000256). The U.S. Government is authorized to reproduce and distribute for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to and where to submit for publication consideration.

## Appendix 1. A 90-year LNT Chronology: From mutation to cancer risk assessment

| Statement | Year |
|---|---|
| First report of induced mutation; Gager and Blakeslee | January 1927 |
| Muller report on X-ray induced mutation in Science | July 1927 |
| Muller (and Gager and Blakeslee) presented data on mutations at Genetics Congress | September 1927 |
| Stadler-presentation of X-ray induced mutation in plants-AAAS Conference | December 1927 |
| Muller and Gager and Blakeslee - 5th Genetics Congress proceedings | undetermined date but published before Sept. 15, 1928 |
| Muller - presentation to National Academy of Sciences on X-ray induced mutations | April 24, 1928-pub. Sept. 15, 1928 |
| Stadler - publication of mutation data in Science | August 24, 1928 |
| Muller - publication of mutation data in PNAS; in this publication he cited the proceedings of the 5th international genetics congress with correct page numbers but with a 1927 publication date which was incorrect. | September 15, 1928 |
| Alex Olson and Gilbert Lewis - proposed linear dose response for mutation to be mechanism of evolution; published in Nature | 1928 |
| Oliver (Muller student) dissertation showing linear dose response for radiation induced mutations | 1930 |
| Muller proposes Proportionality Rule | 1930 |
| Stadler challenges Muller on gene mutation interpretation for reported transgenerational phenotypic changes induced by ionizing radiation. Challenge based on novel cytogenetic advances of McClintock. | 1931 and then at 1932 6th international Genetics Congress |
| Timofeeff-Ressovsky et al. propose single hit model and link to Muller's linear dose response mutational data | 1935 |
| McClintock demonstrates new mechanism for radiation-induced mutation | 1935 |
| Ray-Chaudhuri (Muller's student) dissertation supports total dose/linear theory | 1939 |
| Manhattan Project-genetic mutation study starts at U. Rochester with Curt Stern directing project | 1943 |
| McClintock develops the transposition gene theory – new mutation mechanism | 1944 |
| Ernst Caspari's data support threshold rather than linear dose response in Manhattan Project research with Curt Stern | fall 1946-Muller sent data (November 1946) |
| Muller receives Nobel Prize for 1927 findings – misleads Nobel audience in lecture on dose response | December 1946 |
| Stern fails to adequately replicate Caspari study with Delta Uphoff | 1946–1948 |
| Stern published Warren Spencer and Caspari papers in Genetics | January 1948 |
| Salvador Lauria (future Nobel prize recipient) tries to convince Muller to incorporate McClintock's transposon findings into mutation theory | 1948 |
| Stern and Uphoff publish mini-meta analysis of Manhattan Project mutation research in Science | 1949 |
| Robley Evans, MIT, supports threshold model, based, in part, on Caspari threshold evidence in a Science publication | 1949 |
| Muller tries to get Stern to challenge Robely Evans; fails on this and then writes articles misrepresenting the Caspari control group data | 1950 and repeats this argument again in 1954 |
| Edgar Altenburg tries to convince Muller to incorporate McClintock's tranposon model into gene mutation theory | 1952 |
| Stadler criticizes Muller gene mutation explanation and single hit model in Science | 1954 |
| National Academy of Sciences BEAR I Genetics Panel, 1955–1956 recommend switch to LNT, misrepresent findings in Science paper and later refuse to provide scientific justification for their recommendation | Summer 1956 |
| NCRPM applies LNT model for cancer risk assessment | December 1958 |
| William L. Russell (Oak Ridge National Labs) published first evidence of dose rate for mutations with ionizing radiation, suggesting the existence of DNA repair | December 1958 |
| NAS BEAR II Genetics Panel, report acknowledges dose rate in mouse and Drosophila | 1960 |
| Russell and Muller have debates in international advisory committees over the role of dose rate in human risk assessment | 1963–1965 |
| Muller dies | April 1967 |
| Russell publicly renounces radiation genetics dose response mantra | 1969 and 1970 based on dose rate findings |
| NAS creates BEIR I (1970) which retains LNT while rejecting total dose; it switches to use of Russell mouse data from fruit fly reliance. Committee is unaware of significant error in Russell control group data | report in 1972 |
| EPA adopts LNT based on the use of the Russell data (which is still in error) | 1975 and reaffirms it in 1977 |
| EPA adopts single-hit LNT model for radiation and chemical carcinogen risk assessment, incorporating an independence of background modeling feature | 1979 – notice in Federal Register |
| EPA switches from single-hit to multi-stage model for cancer risk assessment | November 1980 |
| EPA adopts additive to background assumption for cancer risk assessment, drops independent to background | 1986 – EPA cancer guidelines |
| Paul B Selby reports error in Russell control group in 1995; error confirmed by the Russells and corrected in the scientific literature separately by Russells [140] and Selby [144,145] | 1996 and 1998 |
| Calabrese applies Russells' and Selby corrections to BEIR 1972 risk assessment and reports that a threshold or hormesis response would have been reported if the control group error had been detected and corrected at the time of BEIR I | 2017 |

## Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.cbi.2018.11.020.



ED_002751_00030339-00017

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cbi.2018.11.020.

## References


[1] R.E. Albert, Carcinogen risk assessment in the U.S. Environmental protection agency, Crit. Rev. Toxicol. 24 (1994) 75–85.
[2] E. Altenburg, Altenburg letter to Muller, Lilly Library, Manuscripts Department, Muller mss, 1958 Indiana University, Bloomington, IN. December 27, 1958.
[3] American Philosophical Society (APS), Caspari letter to Stern. Stern papers, Caspari File, (September 25, 1947).
[4] American Philosophical Society (APS), Caspari letter to Stern. Stern papers, (November 7, 1947) , Accessed date: 7 November 1947.
[5] American Philosophical Society (APS), Stern Letter to Caspari. Stern Papers, Caspari File, Fall 1947, Undated, (1947).
[6] Anonymous, Dr. Donald R. Charles Mourned by Educators, Rochester Democrat and Chronicle, 1955 Wednesday, November 30, 1955.
[7] Anonymous, (Genetic panel, W. Weaver, chair). National Academy of sciences (NAS), biological effects of atomic radiation (BEAR), genetic effects of atomic radiation, Science 123 (1956) 1157–1164.
[8] G.W. Beadle, Memo to Genetics Committee, American Philosophical Society, Philadelphia PA, 1956 August 24.
[9] G.W. Beadle, Letter to Detlev Bronk, American Philosophical Society, Philadelphia PA, 1957 September 11.
[10] R.H. Beyler, Targeting the organism: the scientific and cultural context of Pascual Jordan's quantum biology, Isis 87 (2) (1996) 248–273.
[11] R.D. Bruce, W.W. Carlton, K.H. Ferber, D.H. Hughes, J.F. Quast, D.S. Salsburg, J.M. Smith, Members of the Society of Toxicology ED01 task Force, W.R. Brown, M.P. Cramner, et al., Re-examination of the ED01 study why the society of toxicology became involved, Fund. Appl. Toxicol. 1 (1981) 26–128.
[12] N.J. Bunce, R.B.J. Remillard, Haber's rule: the search for quantitative relationships in toxicology, Hum. Ecol. Risk Assess. 9 (6) (2003) 1547–1559.
[13] E.J. Calabrese, The road to linearity at low doses became the basis for carcinogen risk assessment, Arch. Toxicol. 83 (3) (2009) 203–225.
[14] E.J. Calabrese, Key studies used to support cancer risk assessment questioned, Environ. Mol. Mutagen. 52 (8) (2011) 595–606.
[15] E.J. Calabrese, Muller's Nobel lecture on dose-response for ionizing radiation: ideology or science? Arch. Toxicol. 85 (12) (2011) 1495–1498.
[16] E.J. Calabrese, How the US National Academy of Sciences misled the world community on cancer risk assessment: new findings challenge historical foundations of the linear dose response, Arch. Toxicol. 87 (2013) 2063–2081.
[17] E.J. Calabrese, Origin of the linearity no threshold (LNT) dose-response concept, Arch. Toxicol. 87 (9) (2013) 1621–1633.
[18] E.J. Calabrese, The Genetics Panel of the NAS BEAR I Committee (1956): epistolary evidence suggests self-interest may have prompted an exaggeration of radiation risks that led to the adoption of the LNT cancer risk assessment model, Arch. Toxicol. 88 (2014) 1631–1634.
[19] E.J. Calabrese, Cancer risk assessment foundation unraveling: new historical evidence reveals that the US National Academy of Sciences (US NAS), Biological Effects of Atomic Radiation (BEAR) Committee Genetics Panel falsified the research record to promote acceptance of the LNT, Arch. Toxicol. 89 (4) (2015) 649–650.
[20] E.J. Calabrese, On the origins of the linear no-threshold (LNT) dogma by means of untruths, artful dodges and blind faith, Environ. Res. 142 (2015) 432–442.
[21] E.J. Calabrese, An abuse of risk assessment: how regulatory agencies improperly adopted LNT for cancer risk assessment, Arch. Toxicol. 89 (4) (2015) 647–648.
[22] E.J. Calabrese, The emergence of the dose-response concept in biology and medicine, Int. J. Mol. Sci. 17 (12) (2016) 2034, https://doi.org/10.3390/ijms17122034 .
[23] E.J. Calabrese, LNTgate: how scientific misconduct by the US NAS led to governments adopting LNT for cancer risk assessment, Environ. Res. 148 (2016) 535–546.
[24] E.J. Calabrese, The threshold vs LNT showdown. Dose rate findings exposed flaws in the LNT model. Part 1. The Russell-Muller debate, Environ. Res. 154 (2017) 435–451.
[25] E.J. Calabrese, The threshold vs LNT showdown. Dose rate findings exposed flaws in the LNT model. Part 2. How a mistake led BEIR I to adopt LNT, Environ. Res. 154 (2017) 452–458.
[26] E.J. Calabrese, Flaws in the LNT single-hit model for cancer risk: an historical assessment, Environ. Res. 158 (2017) 773–788.
[27] E.J. Calabrese, Was Muller's 1946 Nobel Prize research for radiation-induced gene mutations peer-reviewed? Philos. Ethics Humanit. Med. 13 (2018), https://doi.org/10.1186/s13010-018-0060-5 (in press).
[28] L.A. Campos, Radium and the Secret of Life, University of Chicago Press, Chicago (IL), 2015.
[29] E.A. Carlson, An unacknowledged founding of molecular biology: H.J. Muller's contributions to gene theory, 1910-1936, J. Hist. Biol. 4 (1) (1971) 149–170.
[30] R. Carson, Silent Spring, Houghton Mifflin Harcourt, New York (NY), 1962.
[31] E. Caspari, C. Stern, The influence of chronic irradiation with gamma-rays at low dosages on the mutation rate in Drosophila melanogaster, MDDC-1200, U.S. Atomic Energy Commission, 1947, pp. 1–18. Available Hathi Trust Digital Library https://www.hathitrust.org/.
[32] E. Caspari, C. Stern, The influence of chronic irradiation with gamma-rays at low dosages on the mutation rate in Drosophila melanogaster, Genetics 33 (1948) 75–95.
[33] D.G. Catcheside, Genetic effects of radiation, Adv. Genet. 2 (1948) 271–358.
[34] D.R. Charles, Radiation induced mutations in mammals, Radiology 55 (1950) 579–581.
[35] D.R. Charles, J.A. Tiben, E.M. Otis, A. Grobman, Genetic effects of chronic X-irradiation exposure in mice, Genetics 46 (1961) 1.
[36] H. Chick, An investigation of the laws of disinfection, J. Hyg. 8 (1908) 92–158.
[37] J.F. Crow, Letter to Weaver. Lilly Library, Muller Mss, Manuscript Department, Indiana University, Bloomington IN, USA, 1956 March 7.
[38] J.F. Crow, Letter to Weaver. Lilly Library, Muller Mss, Manuscript Department, Indiana University, Bloomington IN, USA, 1956 March 12.
[39] J.F. Crow, Letter to Weaver. Lilly Library, Muller Mss, Manuscript Department, Indiana University, Bloomington IN, USA, 1956 March 29.
[40] J.F. Crow, Letter to Muller. Lilly Library, Muller Mss, Manuscript Department, Indiana University, Bloomington IN, USA, 1962 July 19.
[41] J.F. Crow, S. Abrahamson, Seventy years ago: mutation becomes experimental, Genetics 147 (1997) 1491–1496.
[42] J.A. Crowther, The action of X-rays on *Colpidium colpoda*, Proc. R. Soc. Ser. B 100 (704) (1926) 390–404.
[43] B. De Bont, N. van Larebeke, Endogenous DNA damage in humans: a review of quantitative data, Mutagenesis 19 (3) (2004) 169–185.
[44] M. Delbruck, Radiation and the hereditary mechanism, Am. Nat. 74 (753) (1940) 350–362.
[45] M. Demerec, Letter to Muller. Muller Mss. Lilly Library, Indiana University, Bloomington IN, 1953, Accessed date: 11 May 1953.
[46] H.H. Dixon, Cosmic radiation and evolution, Nature 123 (3113) (1929) 981.
[47] H.H. Dixon, The mechanism of variation, Nature 125 (3165) (1930) 992–993.
[48] H.E. Driver, I.N.H. White, W.H. Butler, Dose-response relationships in chemical carcinogenesis – renal mesenchymal tumors induced in the rat by single dose dimethylnitrosamine, Br. J. Exp. Pathol. 68 (2) (1987) 133–143.
[49] N. Finney, Fallout Peril Found Less Severe. Danger in Genetics Overrated 4 Times, Research Discovers, Buffalo Evening News, 1958, p. 1958 Friday, December 19.
[50] N.G. Fossett, B.J. Byrne, S.J. Kelley, A.R. Tucker, P. Arbour-Reily, W.K. Lee, The influence of large deletions on the mutation frequency induced by tritiated water and X-radiation in male *Drosophila melanogaster* post-meiotic germ cells, Mutat. Res. 307 (1994) 213–222.
[51] E. Fratini, B. Amendola, Caves and other subsurface environments in the future exploration of Mars: the absence of natural background radiation as biology concern, Rendiconti Lincei. Sci. Fis. Nat. 25 (Suppl 1) (2014) 891–896.
[52] J. Furuno-Fukushi, K. Masumura, T. Furuse, Y. Noda, M. Takahagi, T. Saito, Y. Boku, H. Suzuki, A. Wyndham-Boris, T. Nohmi, et al., Effect of *Atm* disruption on spontaneously arising and radiation-induced deletion mutations in mouse liver, Radiat. Res. 160 (2003) 549–558.
[53] C.S.A. Gager, A.F. Blakeslee, Chromosome and gene mutations in Datura following exposure to radium rays, Proc. Natl. Acad. Sci. U.S.A. 13 (1927) 755–779.
[54] B. Glass, Memo to the Committee on Genetic Effects of Atomic Radiation, American Philosophical Society, Philadelphia PA, 1956 November 26.
[55] T.H. Goodspeed, A.R. Olson, The production of variation in nicotiane species by x-ray treatment of sex cells, Proc. Natl. Acad. Sci. 14 (1928) 66–69.
[56] J.B.S. Haldane, Report on Mr. Ray-Chaudhuri's Thesis. Muller Mss, Lilly library, University of Indiana, Bloomington, IN, 1939.
[57] F.B. Hanson, The effect of X-rays in producing return gene mutations, Science LXVII (1928), https://doi.org/10.1126/science.67.1744.562 562-562.
[58] F.B. Hanson, Radiation-genetics, Phys. Rev. 13 (4) (1933) 466–496.
[59] F.B. Hanson, F. Heys, Effects of radium in producing lethal mutations in *Drosophila melanogaster*, Science 68 (1753) (1928) 115–116.
[60] F.B. Hanson, F. Heys, An analysis of the effect of the different rays of radium in producing lethal mutation in *Drosophila*, Am. Nat. 63 (1929) 201–213, https://doi.org/10.1086/280154.
[61] F.B. Hanson, F. Heys, A possible relation between natural (earth) radiation and gene mutations, Science 71 (1828) (1930) 43–44.
[62] F.B. Hanson, F. Heys, Radium and lethal mutations in *Drosophila* further evidence of the proportionality rule from a study of the effects of equivalent doses differently applied, Am. Nat. 66 (1932) 335–345, https://doi.org/10.1086/280441.
[63] F.B. Hanson, F. Heys, E. Stanton, The effect of increasing X-ray voltages on the production of lethal mutations in *Drosophila melanogaster*, Am. Nat. 65 (1931) 134–143, https://doi.org/10.1086/280355.
[64] A. Hollaender, Letter to H. Andrews, NCI, February 7, American Philosophical Society, 1960.
[65] M.R. Jaenen, The Cranberry Scare of 1959: the Beginning of the End of the Delaney Clause. Dissertation, Doctor of Philosophy, Texas A&M University, 2010 December 2010.
[66] Joint Committee on Atomic Energy (JCAE) of the Congress of the United States, Hearings on the Nature of Radioactive Fallout and its Effects on Man. 2 Vols, Plus Summary, Government Printing Office, Washington DC, 1957.
[67] M. Kawanishi, K. Okuyama, K. Shiraishi, Y. Matsuda, R. Taniguchi, N. Shiomi,




ED_002751_00030339-00018

M. Yonezawa, T. Yagi, Growth retardation of paramecium and mouse cells by shielding them from background radiation, Radiat. Res. 55 (2012) 404–410.
[68] K. Koidsumi, Quantitative studies on the lethal action of x-rays upon certain insects, J. Soc. Trop. Agric. 2 (3) (1930) 243–263.
[69] S. Kondo, Mutation and cancer in relation to the atomic-bomb radiation effects, Jpn. J. Canc. Res. (Gann) 79 (1988) 785–799.
[70] G. Lefevre, A comparison of x-ray induced genetic effects in germinal and somatic tissue of *Drosophila melanogaster*, Degree of Doctor of Philosophy, Graduate School of the University of Missouri, 1949.
[71] G. Lefevre, X-ray induced genetic effects in germinal and somatic tissue of *Drosophila melanogaster*, Am. Nat. 84 (818) (1950) 341–365.
[72] S.C. Lind, The chemical effects of radium radiation, Am. J. Roentgenol. Radium Ther. 21 (1929) 480–482.
[73] L. Lindahl, The Croonian lecture, 1996: endogenous damage to DNA, Phil. Trans. Biol. Sci. 351 (1347) (1996) 1529–1538.
[74] S.E. Luria, A Professor Takes Exception. The Boston Globe, (1962) , Accessed date: 2 July 1962.
[75] R.H. Lutts, Chemical fallout: Rachel carson's silent spring, radioactive fallout, and the environmental, Environ. Rev. 9 (3) (1985) 210–225.
[76] N. Mantel, W.R. Bryan, Safety testing of carcinogenic agents, J. Natl. Cancer Inst. 27 (2) (1961) 455–470.
[77] J.W. Mavor, On the elimination of the X-chromosome form the egg of *Drosophila melanogaster* by X rays, Science 54 (1921) 277–279.
[78] J.W. Mavor, The production of nondisjunction by X rays, Science 55 (1420) (1922) 295–297.
[79] J.W. Mavor, The production of nondisjunction by X rays, J. Exp. Zool. 39 (2) (1924) 381–432.
[80] B. McClintock, A cytological and genetical study of triploid maize, Genetics 14 (1929) 180–222.
[81] B. McClintock, Chromosome morphology in Zea mays, Science 69 (1929) 629.
[82] B. McClintock, Cytological observations of deficiencies involving known genes, translocations and an inversion in *Zea mays*, Mo. Agric. Exp. Stn. Res. Bull. 163 (1931) 1–30.
[83] I. Menzies, Prof Says Mutations Just Won't Be Born, The Boston Globe, 1962, p. 9 June 19.
[84] F.J. Miller, P.M. Schlosser, D.B. Janszen, Haber's rule: a special case in a family of curves relating concentration and duration of exposure to a fixed level of response for a given endpoint, Toxicology 149 (2000) 21–34.
[85] H.J. Muller, Effects of X-radiation on genes and chromosomes, Read at the AAAS Conference in Nashville, Tennessee, December 1927. Lilly Library, Muller mss, Indiana University, Bloomington IN, 1927.
[86] H.J. Muller, Artificial transmutation of the gene, Science 66 (1927) 84–87, https://doi.org/10.1126/science.66.1699.84.
[87] H.J. Muller, The problem of genic modification. Verhandlungen des V. Internationalen Kongresses Fur Vererbungswissenschaft (Berlin, 1927). Zeitschrift Fur inductive abstammungs- und Verbungslehre, vol. 1, Suppl Band, 1928, pp. 234–260.
[88] H.J. Muller, The production of mutations by x-rays, Proc. Natl. Acad. Sci. 14 (1928) 714–726.
[89] H.J. Muller, Radiation and genetics, Am. Nat. 64 (1930) 220–257, https://doi.org/10.1086/280313.
[90] H.J. Muller, Nobel Prize Lecture. Stockholm, Sweden, December 12, (1946).
[91] H.J. Muller, Letter to Stern. Lilly Library. Muller Mss, Manuscript Department, Indiana University, Bloomington IN, USA, 1946 November 12.
[92] H.J. Muller, Letter to Altenburg. Lilly Library. Muller Mss, Manuscript Department, Indiana University, Bloomington IN, USA, 1946 July 8.
[93] H.J. Muller, Letter to Stern. Lilly Library. Muller Mss, Manuscript Department, Indiana University, Bloomington IN, USA, 1947 January 14.
[94] H.J. Muller, Some present problems in the genetic effects of radiation, J. Cell. Comp. Physiol. 35 (Suppl 2) (1950) 9–70.
[95] H.J. Muller, The manner of production of mutations by radiation, in: A. Hollaender (Ed.), Radiation Biology. Volume I: High Energy Radiation, Chapter 8, McGraw-Hill Book Company, New York (NY), 1954, pp. 475–626.
[96] H.J. Muller, How radiation changes the genetic constitution. Proceedings of the International Conference on the Peaceful Uses of Atomic Energy. Volume 11, Biological Effects of Radiation, Held in Geneva Aug 1955, United Nations, New York (NY), 1956, pp. 387–399.
[97] H.J. Muller, Letter to Beadle. Lilly Library. Muller mss, Manuscript Department, Indiana University, Bloomington IN, USA, 1956August 27.
[98] H.J. Muller, Letter to Russell, Lilly Library, Bloomington IN, 1958, Accessed date: 19 December 1958.
[99] H.J. Muller, Synthesis. Genetic today, Proceedings of the XI International Congress of Genetics, the Hague, The Netherlands, September 1963. Radiation Genetics, MacMillan, New York (NY), 1965, pp. 265–274.
[100] H.J. Muller, L.M. Mott-Smith, Evidence that natural radioactivity is inadequate to explain the frequency of "natural" mutations, Proc. Natl. Acad. Sci. 16 (1930) 277–285.
[101] H.J. Muller, Oster II, Principles of back mutation as observed in Drosophila and other organisms, in: G.D. De Hevesy, A.G. Forssberg, J.D. Abbatt (Eds.), Advances in Radiobiology, Oliver & Boyd, Edinburgh (UK), 1957, p. 407.
[102] Mullis K, Faloona F, Scharf S, Saiki R, Horn G, Erlich H. 1986. Specific enzymatic amplification of DNA in vitro – the polymerase chain-reaction. Cold Spring Harbor Symp. Quant. Biol., Part 1 51:23-273. (patent, 1987).
[103] National Academy of Sciences (NAS), The Biological Effects of Atomic Radiation (BEAR II), Summary reports, Washington DC, 1960.
[104] National Academy of Sciences (NAS)/National Research Council (NRC), BEAR I Genetics Panel Transcript, Dated February 5 (Unpublished), (1956).
[105] National Academy of Sciences (NAS)/National Research Council (NRC), The Effects on Populations of Exposure to Low Levels of Ionizing Radiation, National Academy, Washington DC, 1972.
[106] National Committee on Radiation Protection, Measurements (NCRPM), Somatic radiation dose for the general population, Science 131 (1960) 482–486, https://doi.org/10.1126/science.131.3399.482.
[107] J.V. Neel, Letter to Weaver, American Philosophical Society (APS). University of Wisconsin, Philadelphia PA, USA, 1956 April 17.
[108] J.V. Neel, Letter to Weaver, American Philosophical Society (APS). University of Wisconsin, Philadelphia PA, USA, 1956 March 8.
[109] J.V. Neel, Letter to Weaver, American Philosophical Society (APS). University of Wisconsin, Philadelphia PA, USA, 1956 March 16.
[110] J.V. Neel, Letter to Weaver, American Philosophical Society (APS). University of Wisconsin, Philadelphia PA, USA, 1956 April 6.
[111] S.L. Nelson, C.B. Giver, A.J. Grosovsky, Spectrum of X-ray-induced mutations in the human *hprt* gene, Carcinogenesis 15 (3) (1994) 495–502.
[112] S.L. Nelson, I.M. Jones, J.C. Fuscoe, K. Burkhart-Schultz, A.J. Grosovsky, Mapping the end points of large deletions affecting the *hprt* locus in human peripheral blood cells and cell lines, Radiat. Res. 141 (1995) 2–10.
[113] M.G. Nuffer, Additional evidence on the effect of X-ray and ultraviolet radiation on mutation in maize, Genetics 42 (3) (1957) 273–282.
[114] N. Okudaira, Y. Uehara, K. Fujikawa, N. Kagawa, A. Ootsuyama, T. Norimura, E. Saeki, T. Nohmi, E. Masumura, T. Matsumoto, Y. Oghiso, K. Tanaka, K. Ichinobe, S. Nakamura, S. Tanaka, T. Ono, Radiation dose-rate effect on mutation induction in spleen and liver of *gpt* delta mice, Radiat. Res. 173 (2010) 138–147.
[115] C.P. Oliver, The effect of varying the duration of X-ray treatment upon the frequency of mutation, Science 71 (1930) 44–46, https://doi.org/10.1126/science.71.1828.44.
[116] C.P. Oliver, An analysis of the effect of varying the duration of x-ray treatment upon the frequency of mutations, Mol. Gen. Genet. 61 (1) (1932) 447–488.
[117] C.P. Oliver, Radiation genetics, QRB (Q. Rev. Biol.) 9 (4) (1934) 381–408.
[118] A.R. Olson, G.N. Lewis, Natural reactivity and the origin of species, Nature 121 (3052) (1928) 673–674.
[119] Oster II, S. Zimmering, H.J. Muller, Evidence of the lower mutagenicity of chronic than intense radiation in *Drosophila genia*, Science 130 (1959) 1423-1425.
[120] T.S. Painter, Salivary chromosomes and the attack on the gene, J. Hered. 25 (12) (1934) 465–476.
[121] T.S. Painter, The morphology of the X chromosome in salivary glands of Drosophila melanogaster and a new type of chromosome map for this element, Genetics 19 (5) (1934) 0448–0469.
[122] T.S. Painter, A new method for the study of chromosome aberrations and the plotting of chromosome maps in Drosophila melanogaster, Genetics 19 (3) (1934) 0175–0188.
[123] M.S. Park, T. Hanks, A. Jaberaboansari, D.J. Chen, Molecular analysis of gamma-ray-induced mutations at the hprt locus in primary human skin fibroblasts by multiplex polymerase chain reaction, Radiat. Res. 141 (1995) 11–18.
[124] B.L. Parsons, Many different tumor types have polyclonal tumor origin: evidence and implications, Mutat. Res. 659 (3) (2008) 232–247.
[125] J.T. Patterson, The effects of x-rays in producing mutations in the somatic cells of Drosophila, Science 68 (1928) 41–43.
[126] J.T. Patterson, Continuous versus interrupted irradiation and the rate of mutation in drosophila, Biol. Bull. 61 (2) (1931) 133–139.
[127] J.T. Patterson, H.J. Muller, Are "progressive" mutations produced by x-rays? Genetics 15 (6) (1930) 495–577.
[128] H. Planel, J.P. Soleilhavoup, R. Tixador, G. Richoilley, A. Conter, F. Croute, C. Caratero, Y. Gaubin, Influence on cell proliferation of background radiation or exposure to very low, chronic γ radiation, Health Phys. 52 (5) (1987) 571–578.
[129] H.H. Plough, The harmful genetic effects of radiation, J. Natl. Med. Assoc. 54 (6) (1962) 652–657.
[130] At Pugsley, T.H. Oddie, C.R. Eddy, The action of X-rays on certain bacteria, Proc. Roy. Soc. Lond. B 116 (1935) 276–298.
[131] S.P. Ray-Chaudhuri, The validity of the Bunsen-Roscoe law in the production of mutations by radiation of extremely low intensity, Proceedings of the 7th International Congress of Genetics, 246, Edinburgh (UK), 1939.
[132] S.P. Ray-Chaudhuri, The validity of the Bunsen-Roscoe law in the production of mutations by radiation of extremely low intensity, Proc. Roy. Phys. Soc. ( Edinburgh, UK) 62 (1944) 66–72.
[133] W.L. Russell, Letter to Muller, Lilly Library, Bloomington IN, 1958, Accessed date: 19 December 1958.
[134] W.L. Russell, Letter to Muller, Lilly Library, Bloomington IN, 1958, Accessed date: 16 December 1958.
[135] W.L. Russell, Memo to Muller, Lilly Library, Bloomington IN, 1958, Accessed date: 16 December 1958.
[136] W.L. Russell, Summary of the effect of dose rate on the induction of mutations by radiation in the mouse, Environmental Effects of Producing Electric Power. Joint Committee on Atomic Energy, 91st Congress of the United States, Part 1, Appx. 11, Oct and Nov 1969, 1969.
[137] W.L. Russell, Mutagenesis in the mouse and its application to the estimation of the genetic hazards of radiation. Presented at the Conference in 1970 and Published in Proceedings in 1973, Adv. Radiat. Res.: Biol. Med. 1 (1973) 323–334.
[138] W.L. Russell, Reminiscences of a mouse specific-locus test addict, Environ. Mol. Mutagen. 14 (Suppl 16) (1989) 16–22.
[139] L.B. Russell, P.R. Hunsicker, The effect of dose rate on the frequency of specific-locus mutations induced in mouse spermatogonia is restricted to larger lesions: a



ED_002751_00030339-00019

retrospective analysis of historical data, Radiat. Res. 177 (5) (2012) 555–564.
[140] L.B. Russell, W.L. Russell, Spontaneous mutations recovered as mosaics in the mouse specific-locus test, Proc. Natl. Acad. Sci. 93 (1996) 13072–13077.
[141] W.L. Russell, L.B. Russell, E.M. Kelly, Radiation dose rate and mutation frequency, Science 128 (3338) (1958) 1546–1550.
[142] H.M. Schmeck, Radiation study surprises expert. Chronic doses have less genetic effect than acute, research congress hears, N. Y. Times (1958) 1958. August 16.
[143] C.M. Scott, Some quantitative aspects of the biological action of X and gamma ray. Special Report Series, Med. Res. Counc. 223 (1937) 1–99.
[144] P.B. Selby, Major impacts of gonadal mosaicism on hereditary risk estimation, origin of hereditary diseases, and evolution, Genetica 102/103 (1998) [445]–[462].
[145] P.B. Selby, Discovery of numerous clusters of spontaneous mutations in the specific-locus test in mice necessitates major increases in estimates of doubling doses, Genetica 102/103 (1998) 463–487.
[146] A.S. Serebrovsky, N.P. Dubinin, X-ray experiments with drosophila, J. Hered. 21 (1930) 259–265.
[147] H. Simons, Geneticist Denies Fallout Mutations Are Lasting Peril, The Washington Post, June 19 (1962), p. 1962.
[148] W.R. Singleton, The effect of chronic gamma radiation on endosperm mutations in maize, Genetics 39 (1954) 587–603.
[149] W.R. Singleton, Radiation effects on living systems, J. Hered. 45 (1954) 58–64.
[150] P.R. Sloan, B. Fogel, Creating a Physical Biology. The Three-man Paper and Early Molecular Biology, University of Chicago Press, Chicago (IL), 2011.
[151] C. Sonnenschein, A.M. Soto, An integrative approach toward biology, organisms, and cancer, Methods Mol. Biol. 1702 (2018) 15–26.
[152] A.M. Soto, C. Sonnenschein, One hundred years of somatic mutation theory of carcinogenesis: is it time to switch? Bioassays 36 (1) (2014) 118–120.
[153] E.M. Southern, Detection of specific sequences among DNA fragments separated by gel-electrophoresis, J. Mol. Biol. 98 (3) (1975) 503.
[154] W.P. Spencer, C. Stern, Experiments to test the validity of the linear R-dose mutation frequency relation in drosophila at low dosage, Genetics 33 (1948) 43–74.
[155] L.J. Stadler, Some genetic effects of x-rays in plants, J. Hered. 21 (1930) 3–19.
[156] L.J. Stadler, The experimental modification of heredity in crop plants. I. Induce chromosomal irregularities, Sci. Agric. 11 (10) (1931) 557–572.
[157] L.J. Stadler, The experimental modification of heredity in crop plants. II. Induced mutation, Sci. Agric. 11 (10) (1931) 645–661.
[158] L.J. Stadler, On the genetic nature of induced mutations in plants, Proceedings of the Sixth International Congress of Genetics 1, 1932, pp. 274–294.
[159] L.J. Stadler, The gene, Science 120 (3125) (1954) 811–819.
[160] W. Stenstrom, J.T. King, The Bunsen-Roscoe law tested for roentgen rays on mammalian lymphoid cells, Proc. Soc. Exp. Biol. Med. 36 (5) (1937) 597–598.
[161] C. Stern, Significance of mutations. Chapter 22, in: C. Stern (Ed.), Principles of Human Genetics, WH Freeman and Company, San Francisco (CA), 1950.
[162] C. Stern, Production of mutations. Chapter 23, in: C. Stern (Ed.), Principles of Human Genetics, second ed., WH Freeman and Company, San Francisco (CA), 1960.
[163] A.H. Sturtevant, Letter to Weaver. Lilly Library, Muller Mss, Manuscripts Department, Indiana University, Bloomington IN, 1956, Accessed date: 20 February 1956.
[164] G. Taubes, Epidemiology faces its limits, Science 269 (1995) 164–169.
[165] J. Thacker, The nature of mutants induced by ionizing radiation in cultured hamster cells. III. Molecular characterization of HPRT-deficient mutants induced by γ-rays or α-particles showing that the majority have deletions of all or part of the *hprt* gene, Mutat. Res. 160 (1986) 267–275.
[166] J. Thacker, Radiation-induced mutation in mammalian cells at low doses and dose rates, Adv. Radiat. Biol. 16 (1992) 77–124.
[167] J. Thacker, E.W. Fleck, T. Morris, B.J.F. Rossiter, T.L. Morgan, Localization of deletion breakpoints in radiation-induced mutants of the *hprt* gene in hamster cells, Mutat. Res. 232 (1990) 163–170.
[168] N.W. Timofeeff-Ressovsky, The effect of X-rays in producing somatic genovariations of a definite locus in different directions in Drosophila melanogaster, Am. Nat. 63 (85) (1929) 118–124.
[169] N.W. Timofeeff-Ressovsky, K.G. Zimmer, M. Delbruck, Nachrichten von der gesellschaft der wissenschaften zu Gottingen. Uber die nature der genmutation und der genstruktur Biologie Band 1, Nr. 13, (1935).
[170] H. Toyokuni, A. Maruo, K. Suzuki, M. Watanabe, The contribution of radiation-induced large deletion of the genome to chromosomal instability, Radiat. Res. 171 (2009) 198–203.
[171] D. Uphoff, C. Stern, Influence of 24-hour gamma-ray irradiation at low dosage on the mutation rate in Drosophila, MDDC-1492, U.S. Atomic Energy Commission, Hathi Trust Digital Library, 1947, pp. 1–6. Available: http://hdl.handle.net/2027/mdp.39015077311788.
[172] D.E. Uphoff, C. Stern, The genetic effects of low intensity irradiation, Science 109 (1949) 609–610, https://doi.org/10.1126/science.109.2842.609.
[173] A. Von Schwerin, Medical physicists, biology, and the physiology of the cell (1920-1940), in: L. Campos, A. von Schwerin (Eds.), Making Mutations: Objects, Practices, Contexts, vol. 393, Max Planck Institute for the History of Science, Berlin, Germany, 2010Available: http://pubman.mpdl.mpg.de/pubman/item/escidoc:2274393/component/escidoc:2274393/P393.PDF.
[174] B. Voss, B. Falk, Nature of reverse mutations in Drosophila melanogaster, Mutat. Res. 20 (2) (1973) 221–234.
[175] A. Weinstein, The production of mutations and rearrangements of genes by x-rays, Science 67 (1928) 376–377.
[176] H. Witschi, The story of the man who gave us "Haber's law", Inhal. Toxicol. 9 (3) (1997) 201–209.
[177] H. Witschi, Some notes on the history of Haber's law, Toxicol. Sci. 50 (2) (1999) 164–168.
[178] R.W.G. Wyckoff, The killing of certain bacteria by X-rays, J. Exp. Med. 52 (1930) 435–447.
[179] S. Wynchank, The Rockefeller Foundation and its Support of Radiobiology up to the 1970s, Rockefeller Archive Center, Research Reports, 2011 Online http://www.rockarch.org/publications/resrep/rrcontinuealpha.php.
[180] K.G. Zimmer, Ergebnisse und Grenzen der treffertheoretischen Deutung von strahlenbiologischen Dosis-Effekt-Kurven, Biol. Zentralblatt 61 (1941) 78.
[181] E.J. Calabrese, Was muller's 1946 Nobel Prize research for radiation-induced gene mutations peer-reviewed? Philosophy Ethics and Humanities in Medicine 13 (2018), https://doi.org/10.1186/s13010-018-0060-5.
[182] E.J. Calabrese, Muller's Nobel Prize research and peer review, Philosophy Ethics and Humanities in Medicine 13 (2018) 15, , https://doi.org/10.1186/s13010-018-0066-z.



ED_002751_00030339-00020

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 3/2/2019 9:38:04 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: LNT
**Attachments**: CBI-Calabrese-LNT.pdf

Clint:

See my latest and most comprehensive effort to date on the historical foundations of LNT.....please shared with your colleagues.

Ed Calabrese

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 4/3/2019 12:20:46 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: hormesis funding

Clint:

See my recent paper on the funding of hormesis.....as you will see most (by far) has been from governmental agencies, not the private sector, contrary to what most people think.

Ed Calalabrese

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 4/26/2019 12:01:24 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: new idea
**Attachments**: Environmental Cancer-2.docx

Clint:

I have new idea which I think you may find important. I hope to have this published in the near future but wanted you to see it first right away.
I would be pleased to discuss this.

Ed

# A FAILED CANCER PARADIGM: Implications for Cancer Risk Assessment and Patients

Edward J. Calabrese, Ph.D

Department of Environmental Health Sciences

School of Public Health and Health Sciences

University of Massachusetts, Amherst, MA 01003

edwardc@schooolph.umass.edu



ED_002751_00030364-00001

The role of the environment in cancer occurrence has been highly disputed over the past 50 years. In the 1970s it was widely believed that environmental factors may account for up to 80% of human cancers. While this was initially thought to relate to the role of environmental contaminants, It became broadened to include diverse lifestyle factors, including diet, medicines and related factors. More recently, the role of environment in human cancer causation has been further questioned within the context of so-called "Bad Luck" mutations, which are claimed to account for some 70% of human cancers, thus greatly diminishing the belief in a dominant role of the environment in cancer causation, especially in the area of chronic low to very low dose exposures which are common in modern industrial societies. In fact, in the US, substantial reductions in exposure to environmental carcinogens in the air, food and drinking water are generally not associated with decreased tumor incidence, with the exception of smoking which should be seen as high dose carcinogen exposure.

A central issue is why cancer incidence and related deaths have not generally declined despite massive national and worldwide efforts to prevent assumed environmentally induced cancers and similar massive efforts to treat such affected individuals with research based therapeutic approaches. The striking failures to prevent the occurrence of cancer and a similar failure to markedly improve survival of cancer patients suggests that something is fundamentally wrong with current accepted paradigms of cancer. This compels the reevaluation of not only our basic understanding of the biology of cancer but also the functional predictive utility of cellular and animal models in both a qualitative and quantitative sense. It is also suggests that the biostatistical models that used by regulatory agencies to estimate risks at low doses and upon which environmental standards are based may also provide highly unreliable information. Yet, environmental health beliefs and regulatory strategies are based on these approaches, typically without evidence of probing reflection by regulatory



ED_002751_00030364-00002

agencies and other leading groups that seem to be locked into dominating paradigms that have yielded profound scientific and clinical failure.

This situation calls for a top to bottom reappraisal of the "cancer problem". This challenge is central to society. Vast resources have been directed to prevent and cure this devastating disease, without the long hoped for successes. Despite the many collective trillions of dollars spent and vast research advances in many areas over a five decade period the results are so strikingly anemic and so far off the mark to indicate that current fundamental understandings are seriously wrong and in need of a drastic rethinking and midcourse corrections.

As an initial step, there needs to be an objective and sober evaluation of the progress or lack thereof at multiple levels: theoretical, experimental, modeling and therapeutic. Many of these research areas do not typically communicate but there is a need for a genuine integrative new synthesis. In the late 1970s under the administrative and scientific leadership of Eula Bingham, OSHA directed a national effort to develop a general scientific consensus to assess cancer risks from low doses of chemical and physical agents. Hundreds of experts testified with the information then synthesized and integrated, resulting in a massive publication in 1980. This effort was used by regulatory agencies to understand the cancer risk assessment issue and to formulate standard setting and create research priorities. Now some 40 years later it is clear than far more needs to be done; society can not continue along the same path and expect a different and improved outcome. A new national leadership effort should be initiated under the aegis of the EPA and the NCI to address how societal efforts can lead to vastly improved understandings of the causation and successful treatment of cancer. The former OSHA approach would be a good one to revisit as there needs to be a formal means by which agencies such as EPA and NIH/NCI can listen to scientific thought leaders in hopes of making the next 40 year period one in which it can deliver on the massive financial investments made to drastically reduce the incidence of cancer and make its clinical treatments far more successful.



ED_002751_00030364-00003

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 1/15/2019 1:39:31 AM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: see pdf
**Attachments**: Hayes Chapter-Dose Response-1.pdf

Clint:

Attached is a chapter on dose response I wrote from the major toxicology textbook edited by Hayes.
The chapter should be of great and really fundamental interest to EPA and its definition of risk assessment.
I strongly suggest that you take a good look this and share it with your colleagues.
If you have any questions please contact me.

Ed

# 3 Dose–Response
## *A Fundamental Concept in Toxicology*

AQ1

*Edward J. Calabrese*

**CONTENTS**

Introduction ..... 90
Dose–Response: How the Threshold Dose–Response Became Accepted ..... 92
History of the Threshold Dose–Response with Particular Focus on Occupational Radiation Protection ..... 100
Threshold Dose–Response: Theoretical Foundations ..... 102
  Introduction ..... 102
  Relationship between Biological Function and the Number of Atoms Inducing It ..... 102
  Second Law of Thermodynamics and Dose–Response Relationships ..... 103
  DNA Adducts: A Method to Estimate Thresholds and/or Linearity? ..... 104
  Threshold Dose–Response: Dose-Dependent Transitions and Underlying Mechanisms ..... 105
  Plotting Data: A Key Element in the Threshold versus Linearity Debate ..... 107
Challenges to the Threshold Model ..... 109
  Introduction ..... 109
  Challenge #1: LNT and Ionizing Radiation ..... 110
  Challenge #2: Hormesis ..... 113
    Historical Foundations ..... 113
    Biphasic Dose–Responses: Multidisciplinary ..... 115
    Hormesis Database ..... 116
    Defining Hormesis ..... 116
    Hormesis Frequency ..... 117
    Validation of Dose–Response Models ..... 117
    Attempt to Validate the LNT Model: The Megamouse Study ..... 118
    Hormesis: Dose–Time Response (Overcompensation) Studies ..... 119
    Hormesis: Plasticity ..... 120
    Summary of Hormesis Challenges to the Threshold (and Linear) Dose–Responses ..... 121
  Challenge #3: Pharmacology and the Biphasic Dose–Response ..... 122
  Challenge #4: Population-Heterogeneity-Based LNT ..... 124
Issues ..... 125
  Dose–Response versus Dose–Time Response Relationships ..... 125
  Adaptive Response/Pre(Post)-Conditioning/Auto Protection ..... 125
  High-Risk Groups: Dose–Responses ..... 126
  How Physiological Status Affects the Dose–Response: The Anti-Inflammatory Phenotype ..... 126
  Triphasic Dose–Responses ..... 127
  Maximum Tolerated Dose/Dose–Response ..... 127
  Shallow/Steep Dose–Responses ..... 127
  Cumulative Dose–Response versus Dose Rate Response ..... 128
  Carcinogens: Latency and Dose–Response ..... 128
  Epidemiology and the Dose–Response ..... 129
Dose–Response in Perspective ..... 130
Open Letter ..... 131
Questions ..... 132
References ..... 132



H100472_C003.indd 89 2/28/2014 4:21:51 PM
ED_002751_00030366-00001

## INTRODUCTION

What is the most fundamental concept in toxicology? Is there a most fundamental concept in toxicology? If there is, would it affect how toxicology is taught, how textbooks are written and organized, how toxicological research is conducted, and how hazard assessments are designed and executed?

Within this context, if one were to name some of the most significant discoveries in toxicology, what would they be? Would these discoveries assist in clarifying and defining the most fundamental concept in toxicology?

While there has been no published survey on this conjectural topic of the most important discoveries in toxicology, some possibilities might include xenobiotic metabolism, including cytochrome P450, phase 2 detoxification, the induction of mutations and cancer with ionizing radiation and chemicals, the linkage of mutation with cancer, DNA repair, biostatistical assessment of experimental data, receptor biology and cell signaling, epigenetics, intercellular communication, and apoptosis, among others. Each important toxicological discovery is expressed within a dose–response framework that affects critical dose-dependent transitions via physiological, pharmacological, and toxicological mechanisms that account for when, why, and how agents induce effects on biological systems.

The shape of the dose–response guides clinical medicine and therapeutics. It also affects the strategy and design of the hazard assessment, risk assessment processes, and regulatory decisions. The toxicology of the twenty-first-century report of the US National Academy of Sciences [1] is set within a cellular and systems biology framework to derive reliable mechanistic understandings of the dose–response, especially in the low-dose zone. The long-stated euphemism that all roads lead to Rome has its toxicological equivalent. All toxicological discoveries and emerging concepts will lead to improved understandings of dose–response relationships.

Getting the dose–response right is at the core of toxicology. Failure to do so has profound implications for environmental risk assessment, regulatory decisions, as well as drug discovery and success in the clinical trial, therapeutics, and health care. Getting the dose right also affects environmental health with concerns over the effects of agents, such as pesticides, on nontarget species, as well as their persistence and capacity to interact with other agents. The dose–response question is therefore an important one, dominating biomedical themes and social concerns.

The study of the dose–response is broad and complex. To understand the how's and why's of the dose–response requires the capacity to integrate findings from a wide range of highly specialized areas of research. It is very interdisciplinary by nature.

The dose–response is not simply a tool of toxicology; it is much more, being even more expansive than the concept of toxicity per se. Within this framework, knowledge of the dose–response is basic to the assessment of interspecies differences in response to xenobiotics and the survival strategies adopted within the plant and animal domains. Dose–response assessments are, therefore, at the core of not only toxic responses but also adaptive strategies.

The dose–response concept is of such fundamental importance to toxicology that it provides a framework by which toxicology may be defined. The concept of the dose–response implies the need to assess the entire dose–response continuum from very low doses that are seemingly without demonstrable effect to higher doses that cause frank toxic effects and mortality and the underlying mechanisms of these effects. Thus, contrary to what may be broadly believed and typically taught, toxicology is not a discipline that is exclusively concerned with adverse effects. It should be concerned with all processes that affect life, including adaptive responses. Ignoring adaptive responses in the study of toxicology impairs the capacity to develop accurate and more fundamental understandings of the dose–response.

Adaptive responses occur within a dose–response framework. What are adaptive responses? When are they induced? Are there molecular detection systems for the discernment of biological alterations/injuries that affect the upregulation of adaptive responses? How does the induction of the adaptive response, or the failure to do so, affect the dose–response for toxic endpoints? It is not, therefore, possible to separate the concept of adaptive response from that of the toxicological dose–response. These differential concepts are part of an integrated dose–response continuum.

Within this dose–response context, the risk assessment definition of EPA purposefully and explicitly excludes the concept of adaptation and repair. Yet, the concept of risk assessment is entirely dependent upon an understanding of the dose–response, its underlying mechanisms, and how they can be used to predict and estimate responses to toxic substances within the population [2].

This chapter therefore argues for a new and more expansive concept of toxicology, framed within a dose–response perspective that is at its core. The truncating of toxicology into those responses that occur at the so-called high doses, above the traditional threshold, and that deal only with induced pathologies has been its history. This history has suffered from a limited view of the dose–response, a perspective fueled by an incorrect understanding of the dose–response concept and its evolution. With the expansion of the dose–response concept into the area of the biological effects of low-dose exposures, including below-threshold effects, toxicology will interface in new and more integrative ways with related subdisciplines within the biological and biomedical sciences. This perspective offers a broader and more inclusive view while building upon past toxicological research achievements and understandings of dose–response relationships and mechanisms.

Toxicology is a fundamental component of systems biology as essentially all biological disciplines are inherently dependent on the dose–response. The dose–response is at the foundation of cellular messaging, biological regulation, plasticity, cellular and tissue repair, health, dysregulation, and disease. The notion that toxicology is a discipline that is only, or even principally, concerned with adverse health effects is


ED_002751_00030366-00002

too limited. Toxicology needs to encompass the entire dose–response continuum.

The dose–response concept is therefore one that unifies and merges long-held conceptual differences between the disciplines of toxicology and its historical parents of pharmacology and physiology. These once distinct disciplines are being progressively seen differently in light of mechanistic advances and the tools by which they are studied. Toxicology is no longer simply a descriptive discipline; it has become transformed into a mechanistically focused discipline within a dose–response context setting where the lines of former disciplinary demarcations are blurring with striking rapidity.

All biological and biomedical disciplines have been built upon the dose–response concept. The dose–response concept emerged from and has been continuously used by researchers in many fields, including physiology, microbiology, pharmacology, ecology, entomology, biostatistics, radiation biology, radiation medical therapies, genetics, and botany [3–9]. Thus, researchers have historically developed toxicological concepts and frameworks based upon the issues in their own discipline. Such individuals have therefore entered the field of so-called modern toxicology from a broad range of scientific disciplines.

Despite the fact that all of the previous fields utilized the concept of dose–response, toxicology tends to see itself historically as an outgrowth of pharmacology during the middle decades of the twentieth century. Yet, the dose–response was emerging as quickly and often with a stronger dose–response basis in the areas of microbiology, plant biology, and entomology. These areas were important not only because of practical societal consequences, but they could also address dose–response issues more effectively (i.e., more doses, greater sample sizes, more replications) because of the ease and cost-effectiveness of more efficient experimental systems. Such areas were able to accommodate the possibility of developing and exploring broad dose–response relationships. This was not something that the area of whole-animal studies could readily accommodate.

Attempts to develop in vitro testing were initiated as early as the first decade of the twentieth century by Alexis Carrel (Figure 3.1) since he needed to avoid excessive variability in the responses of outbred animals in wound-healing studies [10]. Since there were no inbred rodent strains available at that time, Carrel opted to explore the novel yet imposing area of cell culture. While reliable findings were not easily obtained, these efforts were to play a determining historical role in the success of in vitro research today. These achievements also were important in the historic success of the Salk polio vaccine [11]. Carrel was initially interested in the search for agents that could significantly accelerate wound healing and then later applied these in vitro methods to assess ways in which life span could be increased within a dose–response context.

The challenging issues with whole-animal testing would continue to be the case throughout most of the twentieth century as whole-animal mammalian systems have been expensive, space demanding, and often yielding highly variable

**FIGURE 3.1** French surgeon and biologist Alexis Carrel (1873–1944). (From Commons.wikimedia.org/wiki/File:Alexis_Carrel_02.jpg [PD-US].) AQ2

results. So challenging has been the demands of whole-animal systems, it contributed significantly to the in vitro revolution of the 1980s and the incorporation of high-throughput chemical screenings, in an effort to more cost-effectively prioritize agents for further evaluation. These more recent efforts would have their origin with the extensive work of Carrel and his inspired followers such as Robert Parker and his remarkable work on the polio vaccine.

The dose–response therefore had detailed formulation and evaluation from other *nontoxicological* disciplines, well before the so-called transition of toxicology had been made from pharmacology. In fact, the development of early statistical assessment methods occurred in the first two decades of the twentieth century with the publication of William Gosset's (Figure 3.2) Student's T-test and Sir Ronald Fisher's the analysis of variance [12], both of which had an important roles in the analysis of toxicological data in the second half of the twentieth century. Yet, their important advances were neither inspired by nor directly related to toxicology per se. The dose–response relationships for the use of disinfectants starting with the applications of Joseph Lister for the sterilizing of surgical activities in the 1860s–1870s were based on the discoveries of Louis Pasteur and expanded by the discoveries of Robert Koch that permitted the isolation and culturing of specific bacteria and other microbial species. Koch [13] was the first to assess the capacity of a range of chemical disinfectants in a concentration-dependent manner using pure cultures of bacteria. These findings accelerated developments in the areas of chemical assessment of disinfectants with their applications to public health practices from community drinking water disinfection starting in the first decade of the twentieth century. Detailed dose–response



ED_002751_00030366-00003

FIGURE 3.2 William Sealy Gosset, British statistician. (From Commons.wikimedia.org/wiki/File:William_Sealy_Gosset.jpg [PD-US-not renewed].)

modeling applying the law of mass action to the process of chemical disinfectants for bacteria was also undertaken in the first decade of the twentieth century [14–16]. Such modeling activities lead Chick and Martin [15] to derive concentration–response thresholds for the inhibitory actions of various disinfectants (e.g., mercuric chloride, silver nitrate, and phenol). Moreover, modeling-based threshold interpretations were based on experimental findings in the observable zone. Dose–response principles, practices, and applications were therefore developing in specific disciplines during the later decades of the nineteenth century.

The field of toxicology has tried to assert itself as a basic science just like physiology, pharmacology, genetics, microbiology, botany, and other biological disciplines have done. While toxicology has been largely successful in achieving this goal within the scientific and regulatory communities, its *basicness* is rooted not in a specific biological system (e.g., plant, microbe, animal), level of biological organization (e.g., in vitro, whole animal), or endpoint but in the dose–response concept, its mechanistic understandings, and applications. Ironically, the field of toxicology has inadequately grasped that its core is the dose–response and how this drives the hazard assessment, efficacy evaluation, and public health implications along with providing cellular mechanisms that account for its quantitative features. The dose–response concept not only provides the historical foundation of toxicology but also a fundamental context within which natural selection occurs at multiple levels of biological organization. When seen in a historical perspective, toxicology is a convergence of a broad range of biological disciplines in which dose–response evaluation and understandings are fundamental. That is, there are many differing biological

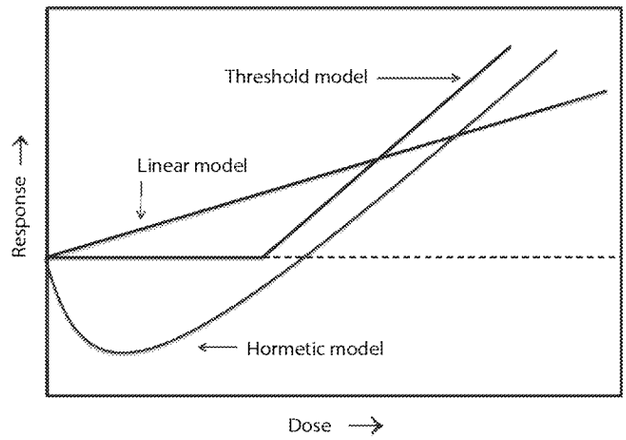



FIGURE 3.3 Most significant contemporary dose–response relationships.

disciplinary paths that require the use of the dose–response concept, modeling of dose–responses, and understanding of mechanisms that can account for the features of the dose–response and that lead to the discipline of toxicology. All are conducting toxicological assessments framed within a dose–response context.

This chapter will also explore the evolution of the dose–response concept for chemicals and radiation, underlying the development of the threshold and linear dose–response models, as well as additional models, such as the biphasic/hormetic (Figure 3.3) dose–response model and polyphasic (e.g., triphasic) models. Within this context, the dose–response concept in homogeneous experimental models will be compared with that of human epidemiology that is characterized by profoundly greater interindividual variation. The hazard assessment process will be assessed ~~on~~ how AQ3
it was employed to validate the threshold dose–response concept that created it, resulting in a toxicological self-fulfilling yet failed prophecy.

The history of the dose–response is a rich one, with scientific, intellectual, and politicized disputes along with dynamic leaders that are far more than historical icons merely listed for completeness in historical assessments. This chapter will explore some of these key historical figures and describe how these intellectual leaders came to formulate the nature of what is called toxicology today, revealing their enormous contributions and perhaps their errors, conflicts, and successes, which have also come to mold and guide the evolution of this field.

## DOSE–RESPONSE: HOW THE THRESHOLD DOSE–RESPONSE BECAME ACCEPTED

The widely acclaimed father of toxicology is Paracelsus. He is especially known for his insightful statement that "the dose determines not only the poison but also the remedy," a concept of dose and response that is extremely broad. This statement implies that the same agent could be both a toxicant


ED_002751_00030366-00004

and one with therapeutic and/or health potential. According to Paracelsus, whether the agent was a toxicant or a tonic depended on the dose. While Paracelsus has long retained an esteemed status in the field of toxicology, his quote has often been truncated by recent generations of toxicologists to yield the following: "the dose determines the poison" [17]. This section explores the original Paracelsian insight into the realm of toxicology, addressing both toxicant and remedy as each is part of the dose–response continuum especially in light of the current experimental developments. It should be appreciated that the views of Paracelsus were not those of a toxicologist but one more closely tied to a philosophical perspective in which all things are interconnected and related. While there were many implications that emerged from this view, the previous idea of chemicals having both beneficial ~~potential~~ and harmful potential that was dependent on the dose was conceptual and intuitive. However, nearly four centuries would have to pass before these speculations could be experimentally tested.

While the concept of the dose–response may appear to be straightforward, it has had a highly controversial history. The first major debate of modern relevance over the dose–response was initiated by Samuel Hahnemann (Figure 3.4), the creator of the practice of homeopathy [18]. Hahnemann was a traditionally trained German physician who became strongly opposed to the medical treatment of his era, a period of the so-called heroic medicine. It was during this period when patients were treated by blood drawing and the administration of often intoxicating doses of heavy metals and other agents. He eventually came to the conclusion that such treatments were often worse than the disease. This led Hahnemann to seek alternative means of treatment that would be both healing and without toxicity. As a result of his intense moral conflict of harming patients while trying to cure them, Hahnemann quit his profession and began to support his family by becoming a professional translator of chemistry and related books. During the course of these translational activities, he developed an insight that was to change his life and lead him to create the medical practice of homeopathy. Based on information learned from reading of the medical literature, Hahnemann developed the belief that medicinal treatments could be obtained from plant extracts to relieve the symptoms of numerous diseases and to enhance healing and recovery from a broad spectrum of diseases and to do so without being toxic.

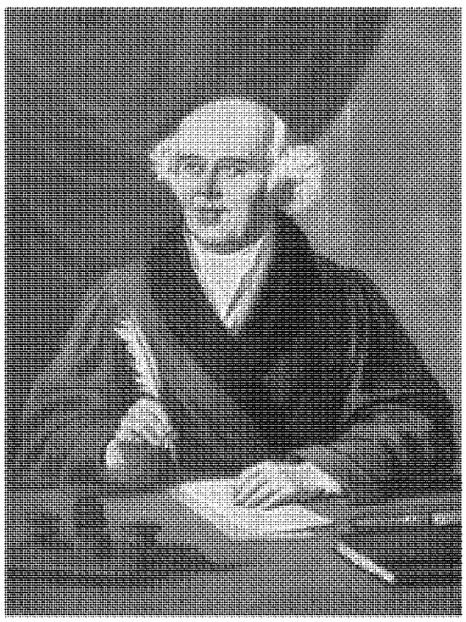


**FIGURE 3.4** Samuel Hahnemann. (From commons.wikipedia.org/wiki/File:Hahnemann.jpg [PD-US-not renewed].)

Hahnemann's drug discovery/medical treatment plan was based upon two principal components: The first was AQ4
an effective drug needed to induce the same symptoms of the disease in healthy subjects that occurred in ill patients (i.e., the like cures like principle). Secondly, the medicinal treatment should be applied at a dose that was not toxic but sufficient to induce an adaptive response (i.e., called by Hahnemann a *vital force* that has been misrepresented to be an amorphous/undefined spiritual phenomenon). The general foundation of this dose–response concept is similar to that put forth centuries before by Paracelsus. However, over time, Hahnemann altered his dose–response concept, making it profoundly less acceptable to scientifically minded individuals by arguing that adaptive responses could be induced at infinitesimally lower doses. This high-dilution drug treatment position became untenable once Avogadro's number became quantifiably clarified in the early part of AQ5
the twentieth century [19]. Using chemical molecule calculations based on Avogadro's number, it was shown that Hahnemann's extremism was indeed real, as many of his homeopathic preparations were estimated to have vanishing few, if any, molecules. Unease with this infinitesimal dosing/therapeutic practice had already been festering even during the life of Hahnemann who died in 1843. In fact, one of Hahnemann's former students was well known for challenging this infinitesimal dosing perspective [20]. Reflecting such disputes, it is clear that by the later decades of the nineteenth century, homeopathy, as a profession, had split into two main groups: the followers of Hahnemann (i.e., the high-dilution group) and those not accepting this view (i.e., the low-dilution group) but still accepting his first concept (i.e., law of similars). By the early 1880s, the high-dilution group represented only a small minority (<10%) of the homeopathy practitioners [18,21]. In practice however, many homeopaths actually tended to straddle the fence, being fiscally pragmatic, selling therapeutic preparations from both practitioner camps.

Despite this fracturing of the field of homeopathy, opponents of this practice, especially those within the field of traditional medicine, have invariably attempted to portray this entire profession as belonging to the Hahnemann *wing* of the movement. Why? Most likely, this was because the dose–response extremism of high-dilution homeopathy was an effective target. By lumping the entire practice


ED_002751_00030366-00005

of homeopathy into the same dose extremism, it was easy to marginalize the entire field. The dose–response concept therefore that emerged from the work of homeopathy based on the early (i.e., prior to the adoption of infinitesimal dose scheme) writings of Hahnemann was that of a biphasic dose–response. The understanding of the dose–response during this time period was far more conceptual than experimentally based. In fact, this perspective was based on limited human exposure studies by Hahnemann and his school in a process called *proving*. Needless to say, by the time that Hahnemann died, the scientific basis of the dose–response was still fundamentally unexplored, lacking the technical capacity and resources for evaluation, especially on a reliably larger scale. However, this would change over the next 50 years with the onset of scientific advances in Europe, especially with the influence of the emerging fields of physiology, pharmacology, and toxicology.

While the well-known biologist Claude Bernard (Figure 3.5) introduced the concept of a threshold dose–response in the mid-1860s, relating to renal excretion [22], there was little serious scientific research concerning the nature of the dose–response until a report emerged from the laboratory of Hugo Schulz in the mid-1880s [23,24] (Figure 3.6). Schulz, a physician, as well as an expert in toxicology and pharmacology, became a highly polarizing figure when he reported that multiple chemical disinfectants not only inhibited yeast metabolism in a dose-dependent manner but also enhanced it at low concentrations, that is, below the toxicity threshold [25]. In his autobiography, Schulz ([26]; see Crump 2003 translation) noted that at first, he did not accept the low-dose stimulation response as real but probably the result of an experimental artifact. However, replication

**FIGURE 3.5** Claude Bernard. (From commons.wikipedia.org/wiki/File:Claude_Bernard.jpg [PD-US-not renewed].)

**FIGURE 3.6** Hugo Schulz (1853–1932). (From http://dose-response.org/low-dose/scientists/schulz.htm.) AQ6

experiments revealed a reliable consistency of the biphasic dose–response:

> Since it could be foreseen that experiments on fermentation and putrescence in an institute of pathology would offer particularly good prospects for vigorous growth, I occupied myself as well as possible, in accordance with the state of our knowledge at the time, with this area. Sometimes, when working with substances that needed to be examined for their effectiveness in comparison to the inducers of yeast fermentation, initially working together with my assistant, Gottfried Hoffmann, I found in formic acid and also in other substances the marvelous occurrence that if I got below their indifference point, i.e., if, for example, I worked with less formic acid than was required in order to halt the appearance of its anti-fermentive property, that all at once the carbon dioxide production became distinctly higher than in the controls processed without the formic acid addition. I first thought, as is obvious, that there had been some kind of experimental or observation error. But the appearance of the overproduction continually repeated itself under the same conditions. First I did not know how to deal with it, and in any event at that time still did not realize that I had experimentally proved the first theorem of Arndt's fundamental law of biology [26].

While none of these observations should have been controversial, they became the object of intense scrutiny, debate, and ridicule. Why was this the case? Schulz made them so by claiming that he had discovered the underlying principle of homeopathy. Schulz set forth the premise that homeopathic remedies act by inducing adaptive responses that enhanced the capacity of biological systems to resist a broad range of environmental insults. The conclusion of Schulz was based on several lines of converging thoughts.



ED_002751_00030366-00006

On the clinical side, there was a report in 1884 by Bloedau [27] that the homeopathic drug veratrine was successful in the treatment of gastroenteritis. Schulz [28] tried to verify that this botanically derived drug could actually kill the disease-causing agent. However, Schulz was unable to verify that this agent could kill the bacterial agent based upon considerable laboratory studies. Since the veratrine failed to kill the disease-causing agent in his laboratory but was apparently successful in the treatment of this disease in people, Schulz hypothesized that the drug acted not by killing the bacteria but by enhancing the adaptive capacity of the individual. While there could have been alternative explanatory possibilities proposed, Schulz then applied his biphasic dose–response observations with the yeast to account for the protective effect of the veratrine in people. It was by this linkage of the biphasic dose–response to homeopathy and its hostile relationship with traditional medicine that it (i.e., the biphasic dose–response) became the object of suspicion, hostility, and marginalization by the medical community starting in 1885 and continuing throughout the twentieth century [29–31].

Schulz [32] made this dose–response assertion in the midst of an intense rivalry between what is today called traditional medicine and the practice of homeopathy. In effect, he placed his newly observed biphasic dose–response into the homeopathic domain. His actions evoked a profound and prolonged series of professional criticisms and personal attacks as well as criticism of his dose–response model by leaders of traditional medicine as well as the medical faculty at his own institution [33,34]. This dispute about the nature of the dose–response could not have occurred at a worse time for the biological, biomedical, and toxicology communities. Experimental studies in these areas were just beginning, and various scientific concepts, including those related to the dose–response, were in the process of being formulated. The issue of the dose–response therefore was in its concept formation period. However, due to economic, philosophical, scientific, and personal conflicts with homeopathy, traditional medicine was *compelled* to attack all things homeopathic as if they were an enemy. Furthermore, the formation of the American Medical Association was explicitly based in part on the need to counter the growing societal influence of homeopathy. This is a generally underappreciated historical fact and one that had profound implications for the biphasic dose–response. As a result of being drawn into the homeopathy–medicine conflict, the biphasic dose–response concept would become collateral damage, leading to its marginalization and exclusion from medical, pharmacology, and toxicology textbooks, curricula, teachings, clinical practices, and government regulatory testing and evaluation procedures. The conflict with homeopathy and the involvement of the biphasic dose–response in the dispute would ironically play a significant role in the acceptance of the threshold dose–response model by the medical community. How could the rejection of Schluz's biphasic dose–response model have affected the acceptance of the threshold dose–response and, in fact, have even led to it?

**FIGURE 3.7** Alfred J. Clark. (From Clark, D.H., *Alfred Joseph Clark (1885–1941): A Memoir*, C & J Clark Ltd., Glastonbury, England, 1985, 61pp.)

While Schulz had his many detractors, none were so visible and effective as Alfred J. Clark (Figure 3.7), a professor of pharmacology at the University of Edinburgh, a renowned researcher, scholar, an acclaimed textbook author ~~writer~~, and a high-level government advisor. His influence upon the field was deep and pervasive and of long duration. One of Clark's goals was to discredit medical quackery. Unfortunately for Schulz, Clark labeled homeopathy as quackery and linked Schulz with the high-dilution wing of homeopathy, a charge that was demonstrably false [25]. Moreover, Clark vigorously attacked Schulz's biphasic dose–response hypothesis in his highly influential books [35,36] in an attempt to trivialize and marginalize Schulz and homeopathy. Clark also argued that research by Dannenberg [37] established that Schulz's findings could be explained by normal variation and that the low-dose stimulation findings were due to inadequate study design and chance and lack the capacity for replication. However, a reexamination of this critical paper by Dannenberg [37] revealed that it did not replicate the work of Schulz, using concentrations that were some 10–20-fold lower. In addition, the research did not collect data at multiple times, a necessary feature to evaluate Schulz's concentration–time response hypothesis. Thus, the paper was not relevant, yet the unfair criticism of Clark stuck because of his reputation and because Schulz, by temperament, would not usually defend himself and also that he was now several years into retirement. Furthermore, when Clark did have the opportunity to assess a paper that was specifically designed to replicate the experiments of Schulz, he never cited it. In this case, the research of Sarah Branham (Figure 3.8) [38] in the highly visible *Journal of Bacteriology* strongly confirmed the findings of Schulz.



ED_002751_00030366-00007

**FIGURE 3.8** Sara Branham (Matthews) (1888–1962). (Courtesy of Georgia Women of Achievement, Inc., LaGrange, GA, www.georgiawomen.org/_honorees/matthewss/index.html.)

**FIGURE 3.9** Benjamin Minge Duggar. (From www.apsnet.org/about/history/pioneeringplantpathologists/Pages/DuggarBenjaminMinge.aspx [PD].)

Of further importance was that Clark's writings had a long reach, affecting several generations of pharmacologists and toxicologists. Such efforts were important in helping to ensure that the threshold model would be incorporated into research, teaching, and regulation, whereas the biphasic dose–response of Schulz would be excluded.

Over the ensuing next half century (~1885–1935), the so-called battle of the dose–responses was waged. However, it was a complex type of dispute. While many scientists were simply not part of the ideological battle between medicine and homeopathy, others, such as some very influential academic leaders of the British pharmacological community, were [29,39,40]. A review of the history of the dose–response reveals that traditional medicine was an organized, harsh, and powerful opponent for the biphasic dose–response. There is also little question that the lack of an *institutional* capacity for homeopathic activity resulted in researchers such as Schulz being isolated and without an institutional and professional support system.

A detailed accounting of the nonideological leading researchers documenting biphasic dose–responses revealed no tendency to organize around the biphasic dose–response concept or to promote it [8,9]. Most of these early leaders publishing in the area of biphasic dose–responses would transition professionally into other positions of leadership in science that, in effect, drew them away from this dose–response research domain [8,9]. In fact, many of these researchers who had demonstrated the occurrence of biphasic dose–responses were outstanding scientists with extensive reputations. For example, Benjamin Duggar (Figure 3.9) was involved in such research from the late 1890s throughout the first half of the twentieth century, becoming a major scientific feature in the United States and worldwide. Over time, he would become less involved with research and became more active with general academic scientific leadership. However, at the age of 72, following his retirement, he discovered the antibiotic Aureomycin in 1948 [41] and was nominated for the Nobel Prize. Yet he was not involved in the battle between homeopathy and traditional medicine.

The first biomathematical modeling of the hormetic–biphasic dose–response was published by the Cornell University microbiology professor Otto Rahn in 1932 [42]. The methods were based on the earlier modeling of the effects of disinfectants on bacterial survival by Chick [14] and others using the law of mass balance. Rahn [42] cited the extensive data supporting the findings of Schulz/Branham on the effects of metabolic poisons/chemical disinfectants on yeast metabolism. Rahn [42] also highlighted the earlier dissertation by Paul Hofmann [43] that paid very careful attention to the question of dosage and its optimization. In these experiments with 13 different agents, Hofmann reported not only that, at the lower concentrations, there were a larger number of colonies but that the colonies were enlarged.

Experimental proof for the biphasic dose–response was very demanding. First, a threshold response had to be estimated. Then both below- and above-threshold response areas need to be assessed when considering the possibility of a biphasic dose–response. While it may not have been appreciated in the early decades of the twentieth century, there was also a need for greater statistical power in the below-threshold doses. This added further difficulty in proving the reproducibility of the low-dose stimulation.



ED_002751_00030366-00008

There was also the distinct possibility that there was a time component needed to demonstrate a biphasic dose–response. This was an initial finding of Schulz [23,24], Townsend, [44] and others, such as Branham [38] who carefully replicated the original findings of Schulz as noted previously. She clearly demonstrated that there was an initial dose-dependent toxicity/inhibition response, followed by a rebound or overcompensation response at low doses, resulting in the occurrence of the biphasic dose–response relationship (Figures 3.10 through 3.12). If the experiment included only one time measurement at the initial point of inhibition, then the stimulatory response would be missed but also the overcompensation response.

The low-dose stimulatory response was also invariably modest in magnitude, making it more difficult to observe and to replicate. Such a modest stimulatory response placed even more pressure on the need to replicate findings due to their greater inherent uncertainty as compared to high-dose toxicity effects. Thus, the dispute between followers of Schulz and those of traditional medicine about the dose–response was fully impacted by methodological and resource challenges that were needed in order to document the possible occurrence of biphasic dose–responses.

Despite these challenges to the study of biphasic dose–responses, there was a surprising and relatively copious AQ7

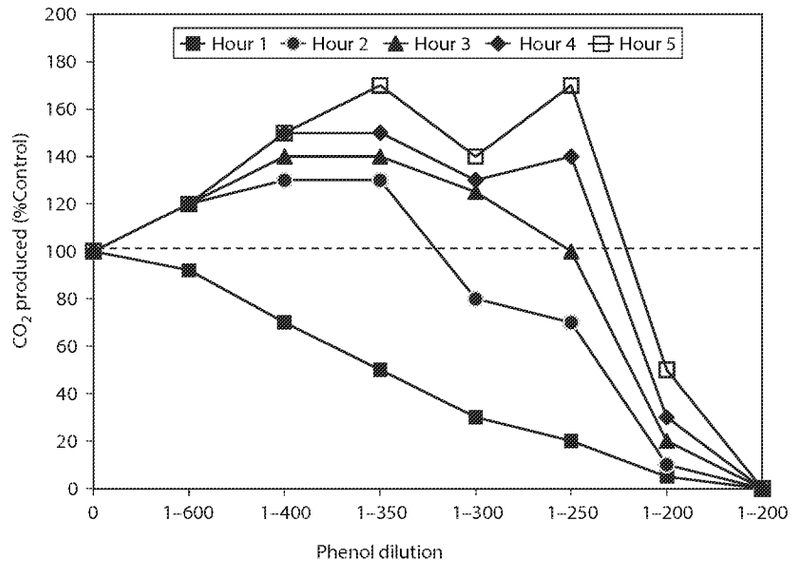



**FIGURE 3.10** The effects of phenol on yeast metabolism. (Based on Branham, S.E., *J. Bacteriol.*, 18, 247, 1929.)

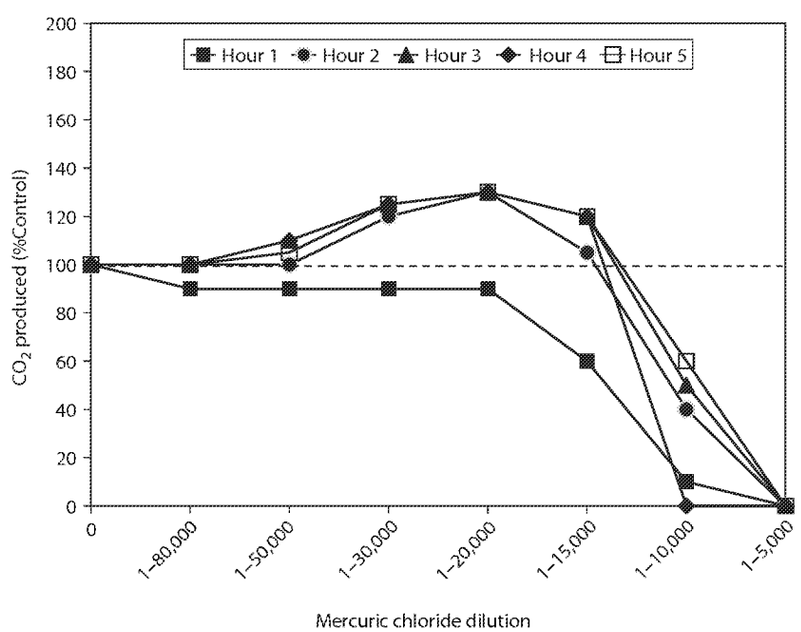



**FIGURE 3.11** The effects of mercuric chloride on yeast metabolism. (Based on Branham, S.E., *J. Bacteriol.*, 18, 247, 1929.)



ED_002751_00030366-00009

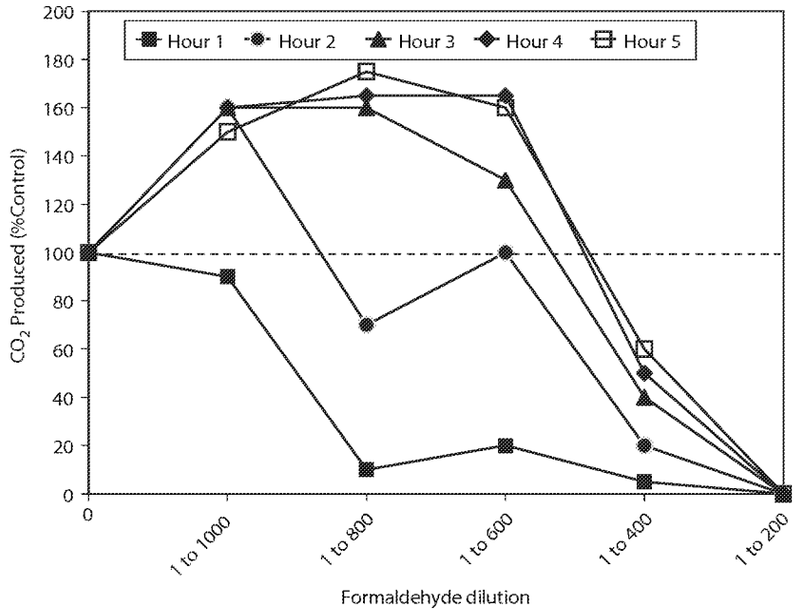



**FIGURE 3.12** The effects of formaldehyde on yeast metabolism. (Based on Branham, S.E., *J. Bacteriol.*, 18, 247, 1929.)

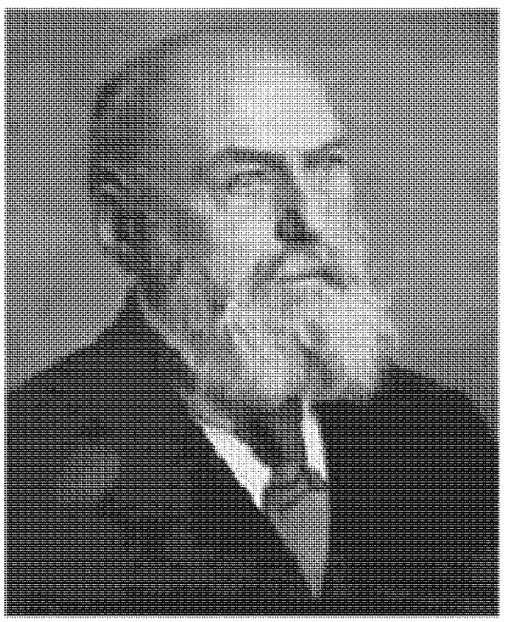
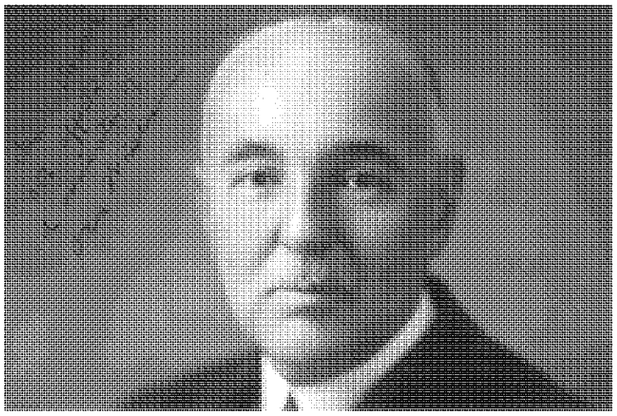


**FIGURE 3.13** Fernando Hueppe. (From dose-repsonse.org/low-dose/scientists/hueppe.htm.)

literature documenting the biphasic dose–response (called the Arndt–Schulz law [32]/or Hueppe's [45] rule (Figure 3.13)) published in leading journals during the early decades of the twentieth century. This research was based principally on work with microorganisms, plants, and insect models. There was also a copious literature in medical journals related to the effects of x-rays on numerous medical conditions such as gas gangrene, arthritis, sinusitis, and otitis media. The publications were typically case reports [46,47], often extensive and supportive of the biphasic dose–responses. The biphasic dose–response concept also became formally integrated into leading textbooks of the first half of the twentieth century for both botany [48] and microbiology [49–52]. However, it was not until 2000 when this historical literature on hormetic–biphasic dose–responses was finally comprehensibly summarized with respect to chemicals [3–7]. Luckey [53,54] had comprehensively addressed the area of radiation hormesis first some 20 years earlier.

While the biphasic dose–response was often observed in the early decades of the twentieth century, it was never the object of an integrative assessment by any of the various researchers of that era. There was no demonstrable understanding or appreciation of the quantitative features of the low-dose stimulation; due to the fact that this stimulation could be both directly induced by a compensatory response, there was no broad discussion concerning the design of experiments to study biphasic dose–responses. This lack of integrative assessment probably resulted from the fact that most researchers with experience in this area, as noted previously, moved on to other professional endeavors. A few researchers, such as Herbert Maule Richards [55,56] at Bernard College, directed a relatively large number of undergraduate students in the study of biphasic dose–responses but never provided a broadly integrative assessment. This was also the case for Charles-Edward Winslow (Figure 3.14), an internationally recognized bacteriologist at Yale University, who directed multiple PhD students in the area of biphasic dose–responses [57–59]. In the case of Winslow, he was to be redirected from dose–response research with bacteria to broader health issues, becoming the editor of the *American Journal of Public Health* and holding that position for about 20 years starting in the mid-1930s. AQ8


ED_002751_00030366-00010



AQ9 **FIGURE 3.14** Charles-Edward Amory Winslow (1877–1957). (From http://www.google.com/imgres?imgurl=http://publichealth.yale.edu/Images/gallery202_74635History.)

The threshold dose–response model had a far easier time in this regard. It was markedly easier to evaluate, had profoundly less challenges with the replication of high-dose toxicity results, required far fewer doses, had smaller sample sizes, and had no complex time component. The threshold concept was also a model that resonated with personal experience. It also had leading researchers, including some in the area of biostatistics, which would advocate for its use and broad-scale applications. Thus, the road was much clearer for acceptance and understanding of the threshold dose–response than with the biphasic dose–response.

By the mid-1930s, the threshold dose–response model had made significant inroads of acceptance with the scientific [60–62] and regulatory communities, serving as the theoretical foundation for how hazard assessment would be conducted and the basis for the derivation of safety factors. While this concept would appear in the 1930s for chemical [63] and radiation safety factors [64], it was not until April 1953 that the safety factor concept became formally part of the FDA [65], the same month that Watson and Creek would publish their proposed structure of DNA. The recommendations of Lehman and Fitzhugh [65] would be broadly accepted affecting how environmental and food health exposure standards would be derived up to the present.

During this time period, the biphasic dose–response failed to become widely accepted, was poorly understood, and also continued to have a strong historical association with the practice of homeopathy, which itself had lost in the battle with traditional medicine in the treatment of patients. Furthermore, homeopathy also was the object of a blistering and profoundly influential attack by Abraham Flexner (Figure 3.15) [66] in 1910 that eventually lead to the closing of almost all the nearly two dozens of homeopathy medical schools in the United States by the early 1920s [67]. In effect, by the end of the 1930s, homeopathy was functionally decimated, and the biphasic dose–response of Schulz was fully marginalized, while the threshold dose–response model had become dominant along with traditional medicine. There were no other competitors.

**FIGURE 3.15** Abraham Flexner. (From http://commons.wikimedia.org/wiki/File:Aflexner21.jpg [PD-US-notrenewed].)

The threshold became the standard dose–response model for industrial chemicals, drugs, and radiation health effects evaluation. It received support from a variety of research perspectives including the occupational work experience for chemicals and ionizing radiation. Of particular importance was that the threshold dose–response model received mechanistic support based on the findings of researchers such as A.J. Clark who was able to demonstrate a relationship between receptor occupancy and the onset of biological effects [68]. He reported a threshold for acetylcholine that required approximately 20,000 molecules acting via receptors to produce an initial effect (i.e., isotonic contraction) on a heart cell. This was an impressive finding and one that Clark would exploit both in his extensive writings concerning the dose–response that would support a threshold model and in his criticism of the Arndt–Schulz law [35,36,69,70]. Therefore, the threshold dose–response appeared to have its foundation on secure scientific grounds. Clark also inspired an extensive series of statistical assessments of dose–response relationships that provided a solid foundation for application to wide-ranging subdisciplines within the biological sciences [71–80].

While the biphasic dose–response would come to have a scientific resurgence from the 1990s to the present, it simply appeared to be a dose–response concept in search of a cause or a proponent—which never seemed to materialize during the early 1900s, even when it was rediscovered and renamed as hormesis in the early 1940s by Chester Southam (Figure 3.16) and John Ehrlich [81] at the University of Idaho. Despite their rediscovery of the biphasic dose–response in research with fungi concerned with the rotting of wood, these two researchers, like so many other early researchers of the biphasic dose–response, soon redirected their focus from



ED_002751_00030366-00011

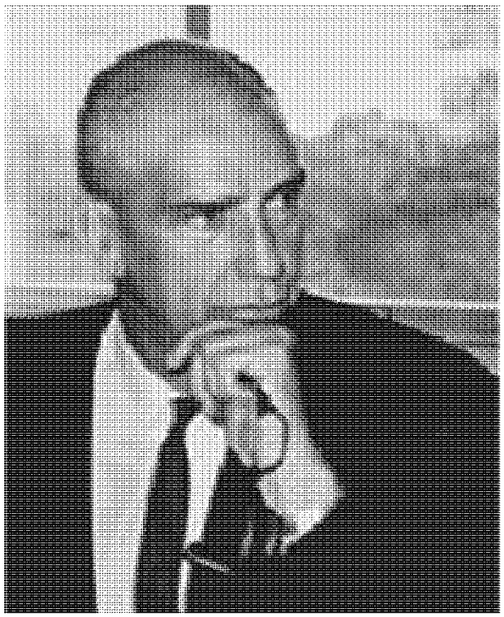


FIGURE 3.16 Chester Southam. (From dose-response.org/low-dose/scientists/southam.htm.)

the dose–response. John Ehrlich moved to the University of Minnesota to work on methods to enhance the production of penicillin during World War II (WWII), later moving to the pharmaceutical company Parke-Davis in Detroit AQ10 to participate in antibiotic/drug discovery activities (i.e., he became quite well known due to his role as a codiscoverer of chloramphenicol; in fact, one of the codiscoverers was nominated for a Nobel Prize). Chester Southam, on the other hand, moved to New York City, graduating medical school from Columbia University, later becoming an expert in the area of tumor antigenicity [8,9]. Thus, the early advocates of the biphasic dose–response model were to come and go, not having the focus and leadership of the medical community that A.J. Clark provided. Despite the dominance of the threshold dose–response and its generalizability, it nonetheless would be challenged during the twentieth century and into the twenty-first century.

## HISTORY OF THE THRESHOLD DOSE–RESPONSE WITH PARTICULAR FOCUS ON OCCUPATIONAL RADIATION PROTECTION

In practical terms, the concept of a *threshold* dose had its origin in the domain of occupational health, with the focus on exposures to ionizing radiation from x-rays and gamma rays. In 1895, Roentgen discovered the x-ray and this ushered in a vast amount of research in a broad range of areas. It was soon learned that x-rays and gamma rays (which were discovered by Becquerel in 1898) could induce a wide range of harmful effects. Despite the early recognition of the hazard potential of ionizing radiation, it would take three decades for the regulatory community to begin to shape a response to this issue. That it might take considerable time to develop an organized response is not surprising given the nature of communications during that era as well as the occurrence of World War I (WWI) and its massive disruptions in Europe and the United States.

An organized assessment of the dose–response due to exposure to ionizing radiation was borne of the creation of the International Committee on X-Ray and Radium Protection by the Second International Congress of Radiology in 1928. The goal of this committee was to advise physicians on radiation safety measures, within a nonregulatory framework [9]. It had nothing to do with the issue of environmental contamination. In 1925, the first International Congress of Radiology met with the intention of renewing communication between opposing countries during the recently ended World War. The US Bureau of Standards provided the liai- AQ11 son function for the United States, selecting Lauriston Taylor (Figure 3.17) as its representative. Taylor, an employee of the Bureau of Standards, would nonetheless act in a voluntary capacity to the international committee without an official US government involvement in the activity. While the bureau would continue to provide the liaison function, the role of the bureau in this domain would become a political issue several decades later as President Eisenhower would create the Federal Radiation Council (FRC) to act as the official US organization with direct accountability in the area.

In parallel to the actions of the international committee, Taylor created a US national committee on radiation protection. This entity was initially called the American X-Ray and Radium Protection Committee. Almost two decades later (1946), after the conclusion of WWII, the name was changed to the National Committee for Radiation Protection

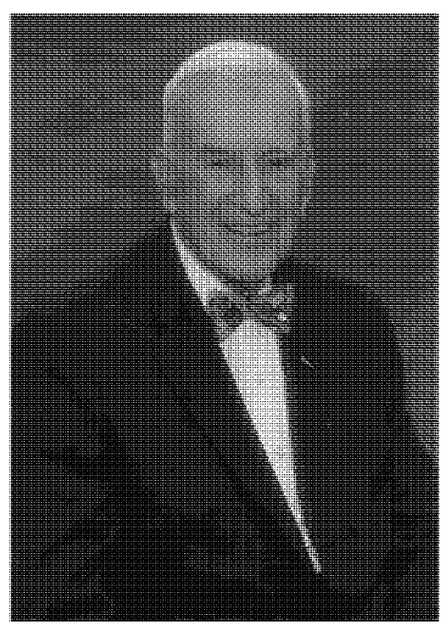


FIGURE 3.17 Lauriston Sale Taylor (1902–2004). (Courtesy of Health Physics Society, McLean, VA, http://hps.org/aboutthesociety/people/inmemoriam/LauristonTaylor.html.)



ED_002751_00030366-00012

and Measurement (NCRPM). This committee was involved in the development of radiation protection standards and in related educational activities within the United States. The initial meeting of this organization was on September 18, 1929. This committee ~~could~~ came to publish documents about various safety procedures and exposure monitoring for workers involved with x-rays and gamma rays [64,82]. It was in the framework of evaluating radium that American X-Ray and Radium Protection Committee, as chaired by Taylor, concluded that the best indicators of ionizing radiation effects were skin changes seen with the fingertips. These areas displayed a reddening and shiny quality of the skin in the zone around the fingernails. An annual cumulative exposure of 600 R (i.e., 0.24 roentgens/day over 250 working days/year) was commonly viewed as the average erythema dose, that is, the exposure that affected a reddening of the skin. The value was obtained via a 1927 poll of radiotherapists. Their collective perspective yielded an average erythema dose of 550 R. The value was then rounded to 600 R in order to adjust for the presence of background scatter radiation [83].

The efforts of this committee of Taylor were preceded by the actions of Mutscheller who first proposed the concept of a tolerance dose for ionizing radiation in 1925, suggesting a value of 1/100 of the erythema dose averaged over 30 days. The approach of Mutscheller [84,85] was practically applied to estimate the quantity of lead shielding needed to protect workers. The concept of tolerance in this case was a type of equilibrium in which there would be a dose to which the workers could be exposed without noticeable harm. From this rather rudimentary start, the tolerance dose concept would proceed and provide the foundation for future radiation safety standards [64,82].

While the credit of first reporting on the concept of a radiation tolerance dose concept goes to Mutscheller, other radiation health experts were independently arriving at the same conclusion [86,87]. While each of these groups proposed a different time interval for the tolerance dose estimation, these values closely converged once similarly normalized. In these cases, the tolerance dose was dependent on the concept of a safety factor to reduce exposure using a fixed fraction of the estimated minimally affecting dose (erythema dose).

During the late 1920s, the International Committee for Radiation Protection (ICRP) offered their version of a tolerance dose for occupational radiation exposure, which was adopted in 1928. This ICRP standard was based on Mutscheller's safety factor of 1/100 of an erythema dose. In fact, it remained the principal basis for international and US prewar radiation standards [83]. The ICRP standard was also principally employed for the calculating of the thickness of lead shielding in x-ray production.

This situation would change during the next decade as Professor Gioacchino Failla (Figure 3.18) of Columbia University Medical School would lead an effort to better understand effects of radium exposures on people and whether safety standards could be derived using skin and blood changes as biological markers. This research suggested that 0.6 R/month would be a safe dose, a value that

**FIGURE 3.18** Gioacchino Failla. (From http://www.orcbs.msu.edu/radiation/resources_links/historical_figures/failla.htm.)

was 10-fold lower than the Mutscheller and ICRP recommendations. Despite the acceptance of the basic clinical findings of Failla and the safety factor concept, the committee agreed upon a higher tolerance dose using a lower safety factor. In this case, the tolerance dose was 0.1 R/day.

The tolerance dose and a threshold dose–response were not believed to be identical by the leaders of this era. The concept of tolerance assumed that there was probably some level of minor harm or damage. However, such assumed minor changes were not thought to be serious enough that they had to be avoided. Thus, the reddening of skin was clearly not a below-threshold response. The observation of reddening skin following radiation exposure was a definitive indication that a biological response threshold had been exceeded. The reddening of skin was used as a biomarker, as a type of warning signal for more serious concerns should the exposure exceed this level. Yet the issue of tolerance and threshold was often functionally confused. The use of a specific numerical limit was often interpreted to mean that there was a threshold of radiation exposure below which no harm would occur.

While the ICRP and other radiation advisory committees were debating the concept of a tolerance dose, thresholds, and skin and blood changes, their field would be turned upside down by a report from Hermann J. Muller (Figure 3.19) that x-rays could cause mutations in the male fruit fly sperm [88,89], which was extended to plants by Stadler [90] within a few months of the Muller report. Furthermore, the findings of mutations as induced by x-rays in fruit flies soon became widely reported by others working in the field [8].

These concept changes failed to be immediately implemented into regulatory guidance-based/exposure practices as committee activities were shut down during WWII. While



ED_002751_00030366-00013

FIGURE 3.19 Hermann Joseph Muller (1890–1967). (From http://en.wikipedia.org/wiki/Hermann_Joseph_Muller [PD-US-only].)

the genetic concerns were raised in the years leading up to the WWII, such issues became dominant in the aftermath of the dropping of the atomic bombs on Japan and activities associated with aboveground testing of nuclear weapons. This set the stage for a long-term debate over the nature of the dose–response in the low-dose zone from ionizing radiation. This debate would be led by the genetics research community under the aegis of the NCRPM, ICRP, and National Academy of Sciences (NAS).

The debate over whether toxicologically based dose–response thresholds exist is a long one, approaching its hundredth year. It is difficult to think of other examples in the scientific literature where a major question still remains as broadly uncertain and contentious and as practically important as ever. On the surface, it would appear that this should not be a particularly difficult problem to resolve. However, this has not proven to be the case. As far as genotoxic carcinogens are concerned, regulatory agencies adopted a precautionary philosophy toward carcinogens based on fear of the cancer endpoint and the possibility that the process of carcinogenesis could be initiated by a single mutagen molecule or ionization in a single cell. This set of concerns gave the assessment and regulation of carcinogens a unique status within society and forced the regulatory agencies to deal with chemical carcinogens and ionizing radiation in a different manner than agents that were not classified as carcinogens. For noncarcinogens, there was believed to be a threshold below which no adverse effect(s) would occur. For genotoxic carcinogens, this was not the case. The regulatory agencies decided to treat them differently assuming there was no safe exposure. The next section will therefore address the theoretical foundations of why the scientific community has long adhered to a belief in a threshold dose–response model. These concepts have involved statistical, thermodynamic, and biological/toxicological domains. The subsequent section will provide a detailed assessment of scientific challenges to the threshold dose–response model, including that initiated by the radiation ~~genetic~~ community that ushered in the linearity at low-dose concept.

## THRESHOLD DOSE–RESPONSE: THEORETICAL FOUNDATIONS

### Introduction

While the threshold dose–response model was adopted without having been validated by the scientific, medical, or regulatory communities during the early decades of the twentieth century, this section of this chapter offers a perspective on what could be the toxicological foundations that would support a threshold dose–response. Five arguments are made with documentation that supports a threshold interpretation. These include the following: (1) there are observations that large numbers of atoms/molecules are needed to induce biological responses; (2) the second law of thermodynamics imposes an energy requirement for chemical reactions to occur, resulting in a threshold; (3) there are pharmacokinetic and pharmacodynamic processes; (4) the use of arithmetic/linear graphing can create a false impression of a linear dose–response, whereas logarithmic dose graphing using molecules/kg/day lead to the conclusion of a distinct threshold for chemical carcinogens; (5) since tumor latency is a function of dose, it is possible to obtain *practical* thresholds for carcinogens, even assuming a linear dose–response relationship.

### Relationship between Biological Function and the Number of Atoms Inducing It

In 1943, George Evelyn Hutchinson [91] (1903–1991), Yale University professor and the father of limnology and modern ecology, explored the relationship of biological functions and the number of atoms required to induce such functions using the liver cell as his model. He provided a listing of various elements from the periodic table and estimated their presence in a human liver cell. Twenty-years later, he provided a considerably expanded view of the number of atoms needed to induce specific liver cell functions [92].

He concluded that it takes the presence of relatively ~~a~~ large number of atoms to affect a response even when there may be a highly evolved biochemical specificity for a reaction to take place. He hypothesized that even at its most sensitive level of activity, the liver cell, as well as probably most cell types, may require more than $10^4$ atoms/molecules per cell. Even in the case of nonnutritive agents, such as Cd and Pb, the number of atoms for each of these agents is $10^6$–$10^8$/liver cell and was associated with no detectable effects.



ED_002751_00030366-00014

Such findings were interpreted by Bertram Dinman [93], a prominent University of Michigan toxicologist, that the presence of specific atoms in a cell does not provide proof of biological activity nor does it offer any biological significance from a beneficial or harmful perspective. Using a complementary approach to Hutchinson [91,92], Dinman [93] concluded that nearly 400 in vitro studies of enzymatic inhibitors for 100 different enzymes [94] revealed that the lowest concentration at which most sulfhydryl enzyme inhibitors act was in the $10^4$–$10^5$ molecules/cell range, a value similar to that proposed by Hutchinson [92]. Taken together, these different approaches lead Dinman [93] to suggest thresholds are the rule in biological systems. Dinman went on to conclude that

> To believe that such molecules cause an undesirable effect disregards the presence of multiplicity of interfering substances. Such thinking also does not take into account the fact that the dose of a foreign atom may be related to the probability of its interacting with an available active site, or that similar probability governs the answers to the question of whether interactions will occur at discrete topographical loci upon a structural or functional molecule (or on a possible precursor). While the construction of stochastically sound models is remote, the reasonableness of the hierarchy of cellular element concentrations as these relate to metabolic function suggests that a threshold for biological activity exists within a cell at $10^4$ atoms.

A practical approach for assessing the threshold issue may be to consider the actual exposure that humans experience from environmental concentrations of well-known toxins. In the case of lead, the CDC has long used 10 μg/100 mL of whole blood as an action level (recently reduced to 5 μg/100 mL). At this concentration of Pb in blood (10 μg/100 mL), there are $3 \times 10^{16}$ Pb atoms. If the exposure standard were to be reduced to 1 μg/100 mL, there would be $3 \times 10^{15}$ Pb atoms per 100 mL, or $3 \times 10^{13}$ Pb atoms/1 mL. It is difficult to consider that at 1 μg/100 mL, a value common today in apparently healthy humans, there are 30-trillion lead atoms for each of the 7500 mL of blood in the average US adult. Such calculations support the existence of an individual and public health threshold for lead.

In a similar fashion, the US EPA benzene drinking water standard of 5 μg/L has an estimated ($1 \times 10^{-5}$) lifetime risk of developing leukemia based on linear nonthreshold (LNT) models. At the drinking water standard of 5 μg/L, there is an estimated $8 \times 10^{15}$ benzene molecules/L. This cosmologically large number is further expanded when one considers that the EPA assumes that 2 L is consumed each day of a 70-year life. These two examples are not exceptions but illustrate the rule as far as the relationship between exposure to atoms/molecules and the onset of adverse health effects are seen in humans. In fact, regardless of whether the regulated agent is a carcinogen or not, the estimate of acceptable exposures is typically in the $10^{-14}$–$10^{20}$ molecules/day for 70 years.

## Second Law of Thermodynamics and Dose–Response Relationships

While individual thresholds are typically observed in toxicological and epidemiological studies, the issue of population-based thresholds has been less certain. This uncertainty is based on the fact that considerable variation exists between individuals with respect to their susceptibility to toxic/carcinogenic agents due to genetics, diet, developmental, and aging processes, among other factors. Thus, apparent thresholds can profoundly differ between individuals. The regulatory challenge therefore may not be that of an individual threshold estimation but a population threshold, thus transforming this question from a biological to a biostatistical one [95,96]. The question therefore is whether there is a population-based threshold for noncarcinogenic toxic substances and carcinogens.

A central fact that underlies the current debate over threshold or LNT for radiation-induced cancer is that each individual experiences cosmic numbers [97] of mutations/cell each day (e.g., depending on the cell type—millions to multiple billions) from normal metabolism and background radiation. If, in fact, a single hit were to be enough to cause cancer, as suggested by the LNT theory, it is difficult to explain why many, perhaps most individuals, would not quickly display various toxicities and/or cancer, unless reasonably efficient repair processes exist.

Despite the fact that vast numbers of mutations occur and are repaired on a daily basis, are there exposures that will not induce genetic damage? According to Schaeffer [96], the second law of thermodynamics provides a basis for such a threshold. This conclusion is founded on the premise that there is a minimum net free energy required for the reaction of an agent (in this case, a toxicant or carcinogen) with a target molecule [98–101]. If the threshold value is diminished, the net free energy that is related to the threshold value would also diminish. However, the net free energy cannot reach or become zero as this can only happen if both the activation energy and the net free energy are zero at all levels of exposure [99,102]. Since chemical bound energy is the "exclusive source of utilizable energy in biological systems, there is a minimum activation energy and a minimum net free energy above zero for all cellular reactions including the induction of cancer." Mutagen binding to DNA affects DNA alterations (i.e., mutagens) and can initiate the process of carcinogenesis. A thermodynamic analysis of this process has yielded a specific energy threshold that needs to be exceeded for the induction of chromosomal aberrations. Such an assessment provides a basis for why each interaction between molecules does not result in a chemical reaction and product formation that could lead to a biological effect. Each xenobiotic agent needs to provide the activation energy to react with the receptor molecule. Using the Maxwell–Boltzmann equation, Koch [103] estimates that the activation energy may vary between 16 and 42 kJ/mol for biochemical reactions in vivo. The minimum net energy required to induce a single strand break


ED_002751_00030366-00015

was estimated to be at least 17 kJ/mol [101], supporting the existence of a threshold.

According to Schaeffer et al. [99], it may be appropriate to use the biological analogy of fertilization of an egg by a sperm when placing the process of chemical carcinogenesis in context. While there are billions of sperm that are present and actively attempting to fertilize the egg, only one does. Furthermore, the process of fertilization requires the presence of massive numbers of sperm. In a similar fashion, chemical reactions take place only where there are sufficient molecules, each displaying kinetic energy, eventually colliding with each other and eventually yielding a novel intermediate molecule that then transforms to the final product. The formation of the reactive intermediate represents a random event within an environment of many millions of molecules. The actions of a carcinogen must therefore be seen as a stochastic process involving massive numbers of targets and a cosmically large numbers of molecules.

Since chemical reactions are subject to entropy and free energy constraints, Schaeffer et al. [99] indicated that mutational effects and carcinogens likewise display activation and free energy requirements as well as entropic dependence. Since entropy represents a statistical estimate of system disorder, these reactions will show the mass requirements of chemical reactions. In fact, therefore, thermodynamic principles lead one to conclude that LNT is both chemical and biologically highly improbable. Pharmacokinetic reasons (absorption, tissue distribution, metabolism, storage, excretion) and the number of molecules that reach a target and thermodynamic parameters that affect molecule activation create the foundation for a physical/chemical/biological basis for biological/toxicological threshold.

This perspective reinforces the previous views of Dinman [93] that there is likely to be a minimal number of atoms/molecules needed to affect biological responses. In fact, the use of the number of Dinman [93] ~~leads~~ Friedman [104] to estimate the minimally inducing number of molecules for various potent carcinogens (i.e., $8.6 \times 10^{15}$ molecules/kg body weight or $10^8$ molecules/kg). Using such analyses, Koch [103] estimated a *response threshold* level for various drinking water contaminants including chemical carcinogens. This modeling considered standard parameters such as average body weight, amount of water consumed/day, molecular conductivity as well as estimates of lipophilicity, and tissue distribution of biological activity. Koch [103] concluded that such outcomes provide not only a theoretical but also a practical means of translating toxicological findings into risk assessment practices. He also emphasized that this perspective illustrates that it is profoundly unrealistic to believe that a single molecule may affect the occurrence of cancer, thereby supporting a threshold dose–response perspective.

Despite their solid underlying foundations, the arguments of Hutchinson [92] and Dinman [93] and similar extensions by Claus [105] and Jukes [106] have not attracted significant formal attention in the literature. However, in 1980, Preussmann [107], a well-known experimental cancer researcher, attempted to apply such concepts to the issue of chemical carcinogen thresholds using the data of Mohr and Hilfrich [108]. In this study, kidney tumors were induced in rats via a subcutaneous (SC) injection of diethylnitrosamine (DENA) using eight different single-dose treatments ranging from 1.25 to 160 mg/kg. They reported 11/20 kidney tumors in the single dose of 100 mg/kg and 1/20 kidney tumors at 1.25 mg/kg. The 1.25 mg/kg dose was the equivalent of 0.3 mg/rat. The control group showed no kidney tumors. The 1.25 mg/kg level of exposure, which was presumably carcinogenic, corresponded to about $2 \times 10^{18}$ molecules/rat or approximately $10^{16}$ molecules/kidney. Assuming the weight of the kidney was about $10^{-10}$ g, Preussmann [107] stated that there was about $10^6$–$10^7$ molecules of DENA/kidney cell at this dose. The $10^6$–$10^7$ molecule number range per cell was about 100–1000-fold greater than the postulated theoretical threshold of $10^4$ molecules/cell.

## DNA Adducts: A Method to Estimate Thresholds and/or Linearity?

As an alternative to the proposition of a theoretical molecule threshold that was postulated by Hutchinson [92], Dinman [93], ~~and~~ Claus [105], Preussmann [107] suggested a more mechanistic approach using DNA adduct biomarkers within susceptible tissue. This approach has demonstrated appeal in the subsequent decades with numerous researchers exploring the relationship of DNA adducts as biomarkers for chemically induced tumors. One of the most integrated of these attempts is seen in the publications of Williams et al. [109,110]. These authors have traced the biological processing of the chemical exposures from the portal of administration through the spectrum of pharmacokinetic processes to pharmacodynamic activity, inducing DNA adduct formation, location of the adducts, and efficacy of DNA repair, and to the route of neoplasmic cell transformations, including the number of mutations, development of tumor microvasculature, and tumor-suppressive elements. The documentation of this type of information was placed in a quantitative perspective, leading Williams et al. [111] to derive a new cell-based mechanism of action that could provide what they called a safe exposure level (SEL) for a DNA-reactive chemical carcinogen; the SEL was based on a DNA binding of less than 1 adduct/$10^9$ nucleotides for a single chemical agent. As suggested previously, the methodology used by Williams et al. [111] follows the administered agent(s) from the beginning to the end stage quantifying all changes that led to the final product and integrating the pharmacokinetic- and pharmacodynamic-mediated information along with tumor development activities.

Starting with an oral exposure to a stable procarcinogen, Williams et al. [111] noted that following ingestion, the agent will be subjected to the risk of degradation caused by chemical and biological processes including gut microflora. Following G.I. absorption, the agent will be transported via the portal blood flow to the liver and undergo the first-pass extraction. For that portion of the dose not taken up by the liver, it will enter systemic circulation, typically


ED_002751_00030366-00016

in a highly diluted manner. For these *escaped* molecules, they become spread out to many organs and their cells, further diluting the dose.

As far as DNA-reactive carcinogens are concerned, the only cells at risk for initiation (and therefore cancer development) are reproducing stem (labile) cells. These cells typically represent <1% of the cell population in any tissue. Another factor affecting exposure to critical cellular sites is that cells display an active extrusion process via p-glycoprotein ATPase to pump hydrophobic cationic agents out of the cell and/or prevent their entry. Williams et al. then generalized that it may be reasonable to assume that perhaps 80% of the *carcinogenic* molecules may be detoxified in the liver. Of the remaining 20% of activated agent, a certain proportion would be *consumed* by encountering any of a wide range of macromolecular nucleophiles in the cytoplasm. In fact, the binding of bioactivated agents is typically much greater in the cytoplasm than nucleus, with a differential of about 100:1.

As each of the activated chemicals reaches the nucleus, it must still contend with the fact that the DNA is enshrouded with nucleophiles that further reduce the potential for mutagenicity. With respect to the cellular genome, it consists of about $3.2 \times 10^9$ base pairs. Within this framework, there are approximately 30,000 genes with an average size of 3,000 base pairs, with about $9 \times 10^7$ functional nucleotides. Up to about six genes would have to be mutated to effectively mediate the process of carcinogenesis [111].

In DNA adduct studies, at low levels of exposure, a relationship between dose and adducts has been shown as follows [111]: aflatoxin, 70 adducts/$10^8$ nucleotides; DMN, 360 or 5/$10^9$ for $N^7$ and $O^6$ methylguanine adducts; and 1/$10^8$ for meIQX. The question arises as to what level of DNA adduct displays biological/toxicological significance. Since spontaneous DNA damage based on labeling studies reveals about 1 lesion/$10^6$ nucleotides, it appears that background DNA adducts are about 10–100-fold greater than that reported in the previous experimental studies.

AQ12

Based on such information, Williams et al. [111] hypothesized that an adduct formation rate of 1/$10^{11}$ should be considered without biological significance. The occurrence of 1 adduct/$10^9$ nucleotides would represent about 3 adducts/cell, at most affecting only 3 of the 30,000 genes/cell. Even with 1 adduct/$10^9$ nucleotides, these authors concluded that there is little biological concern. Further, only a proportion of such adducts will be mutagenic, while others will have their mutagen damage repaired. In addition, not all mutations are of equal concern. Only mutations in certain locations of susceptible genes can alter gene function. Thus, many mutations can be without critical biological effect. For example, the vast majority of mutations of the p53 tumor suppressor gene did not significantly affect the amino acid structure of the protein [112]. Another consideration affecting the development of a tumor cellular mass is the need to circumvent host resistance and to form a neovasculature for expansion to a neoplasm. According to Williams et al. [111], the likelihood that a preneoplastic lesion will progress to a tumor is ≤1/1000. The capacity to progress is a function of dose, which can affect the replication potential of the affected cells and related promotional stimuli. At low doses, these promotional factors are far less evident.

Based on the previous mechanistic approach, Williams et al. [111] have addressed the issue of dose–response in general and the threshold concept in particular. Within this framework, these authors isolated specific stages of the process of carcinogenesis including cell proliferation and the induction of numerous preneoplastic and progressive hepatocellular lesions. For each of these steps, they report the occurrence of a threshold response. These collective factors led Williams et al. [111] to propose a change in the risk assessment of carcinogens—from that of an LNT model to the one that is both mechanism and threshold based using the frequency of DNA adducts as the key molecular endpoint to predict the risk of cancer.

The line of argument that has just been presented is the result of nearly 40 years of detailed toxicological investigations [113]. It confronts the long-held linearity perspective as stated in 1969 by Fahmy and Fahmy [114] that "there seems to be no such thing (i.e., thresholds) as far as mutations are concerned." Even more so, the toxicologist Bruce Ames [115] expanded on this area by stating

> It is worth emphasizing that one molecule of a mutagen is enough to cause a mutation and that if a large population is exposed to a 'weak' mutagen it may still be a hazard to the human germ line, since no repair system is completely effective, there may be no such thing as a completely safe dose of a mutagen.

While these historical cautionary statements of Fahmy and Ames still even now seem prudent, the cumulative findings as presented previously demonstrate that this type of conceptualization is fundamentally flawed stochastically, pharmacokinetically, pharmacodynamically, and thermodynamically.

## Threshold Dose–Response: Dose-Dependent Transitions and Underlying Mechanisms

Within the past decade, there has been a strong consideration given to the topic of dose-dependent transitions in toxicity and how such descriptive changes in the dose–response could be mechanistically explained. The Health and Environmental Science Institute (HESI) conducted several workshops that addressed this issue [116,117]. These efforts were premised on the belief that a range of different mechanisms may occur for a toxic substance across a very broad dose–response range.

Such dose-dependent toxicities could also impact the risk assessment process and need greater clarification. The expert committee identified various processes that might contribute to the occurrence of dose-dependent toxicity transitions. These processes include gastrointestinal (G.I.) tract or respiratory absorption, tissue distribution as affected by protein binding and active transport systems, and chemical


ED_002751_00030366-00017

**TABLE 3.1**
**Mechanistic Basis for Dose-Dependent Transitions in Case Studies**

| Case Study | Mechanism |
|---|---|
| Acetaminophen | Metabolic activation and glutathione depletion |
| Butadiene | Metabolic activation |
| Ethylene glycol | Saturation of oxidation |
| Formaldehyde | Changes in cell kinetics |
| Manganese | Low-dose essentiality and high-dose toxicity |
| Methylene chloride | Metabolic activation |
| Peroxisome proliferator-activated receptor (PPAR) | Receptor activation |
| Progesterone/hydroxyflutamide | Receptor interaction |
| Propylene oxide | Altered homeostasis |
| Vinyl acetate | Altered homeostasis |
| Vinyl chloride | Adduct formation and DNA repair |
| VDC | Enzyme saturation and depletion |
| Zinc | Deficiency toxicity and high-dose toxicity |

*Source:* Slikker, Jr. W. et al., *Toxicol. Appl. Pharmacol.*, 201, 203, 2004.

transformation, including bioactivation and detoxification, receptor interactions, tissue and DNA repair processes, as well as altered homeostasis. Thirteen distinct examples of dose-dependent transitions were identified (Table 3.1) and discussed (Table 3.2). These examples were selected since they affect a broad spectrum of mechanisms such as metabolic activation, altered homeostasis, enzyme saturation and depletion, alteration in cell kinetics, adduct formation and DNA repair, and glutathione depletion.

An instructive example of a dose-dependent transition involved the toxicological assessment of acetaminophen, an agent whose toxicity has been closely associated with a depletion of reduced glutathione (GSH). This depletion begins to occur upon saturation of glucuronidation and sulfation pathways. This saturation process results in more acetaminophen becoming converted to the toxic electrophilic metabolite of acetaminophen called NAPQI. Once formed, the NAPQI becomes quickly detoxified by GSH in the affected tissue, resulting in GSH depletion. At high metabolite doses, the GSH depletion becomes more extreme, leading to occurrence of NAPQI-induced damage. Thus, the central factor in acetaminophen's induced hepatotoxicity involves both

**TABLE 3.2**
**Factors Affecting Dose-Dependent Transitions**

**Dose-Dependent Changes in Excretion**

Considerable research has been conducted concerning the quantitative renal saturation behavior of drugs.

Two types of saturable active transport processes affect the urinary elimination of xenobiotics (tubular secretion and tubular resorption).

Saturation of tubular secretion tends to lower renal clearance at high doses; this results in yielding a larger internal body concentration at higher rates of external dosing.

Saturation of tubular resorption processes displays the opposite effect.

**Dose-Dependent Alterations in Metabolism**

Michaelis–Menten enzyme kinetics.

As activating/detoxifying enzymes have limited capacity, they will become saturated at some elevated dose.

At progressively higher doses, a larger fraction of the xenobiotic is metabolized and may be routed to other pathways.

**Dose-Dependent Changes in Repair, Cell Killing, and Rate of Cell Replication**

Tissue repair.

DNA repair.

Saturation of repair systems at elevated levels of exposure tends to result in longer biological half-lives of the induced lesions and a greater likelihood for the lesion to be incorporated into the genome following DNA replication. This type of process would enhance the incidence of mutations per incident of exposure.

Induction of repair process can also influence the degree of damage retained. It is generally unknown how the dose of mutagens affects the magnitude of the repair induction process and how this may vary between individuals. These factors are likely to affect dose-dependent transitions.

*Source:* Slikker, Jr. W. et al., *Toxicol. Appl. Pharmacol.*, 201, 203, 2004.



ED_002751_00030366-00018

the formation of NAPQI and the tissue's ability to produce adequate amounts of GSH. The acetaminophen-induced hepatotoxicity will be affected by factors that influence that capacity for bioactivation as well as GSH production and regeneration. There is likely to be some degree of interindividual variation in the capacity of acetaminophen to transition into a toxicity mode. Another example of a saturable enzyme involves the metabolism of ethanol by alcohol dehydrogenase (ADH). Once this enzyme becomes saturated, the toxicity response becomes nonlinear. In contrast to the example with acetaminophen, the saturable enzyme is the one that led to detoxification.

Another example of an agent that is metabolized via cytochrome P450-dependent monooxygenases to a metabolite that binds to and depletes GSH is vinylidene chloride (VDC). According to Slikker et al. [116,117], the GSH depletion decreases in proportion to the concentration of the toxic metabolite generated. However, a dose-dependent toxic transition occurs when the GSH has been depleted by 60% that occurs at 50 mg/kg with no toxicity occurring at 25 mg/kg. It was speculated that the 60% GSH decrease may reflect the limits of reserve capacity below which the toxic mechanisms are able to alter plasma membranes leading to frank toxicities.

A particularly interesting example of a dose-dependent transition involved the mechanism by which propylene oxide induces nasal tumors in rats following exposure via the respiratory route [116,117]. Of particular interest was that the nasal tumor incidence reflected a clear threshold dose–response, whereas the occurrence of hemoglobin and DNA adducts followed a linear dose–response relationship and were thus not capable of accounting for the nasal tumor incidence. However, the cell proliferation induced in the nasal respiratory epithelium also followed a similar threshold pattern of the nasal tumors. These findings show a very strong association between cell proliferation and nasal tumor incidence (Figure 3.20).

The dose-dependent cell proliferation model has also been proposed in the assessment of formaldehyde-induced nasal squamous cell carcinoma in rodents. The doses associated with the cancerous responses were those that induced cell death while subsequently stimulating regenerative cellular proliferation (RCP). In a detailed cancer bioassay study with formaldehyde, Monticello et al. [118] employed five concentrations (0.7, 2.0, 6.0, 10.0, and 15.0 ppm) at which RCP was measured at multiple locations in the nasal tissue over days 1, 4, and 10 and at weeks 6, 13, 26, 52, and 78. Of particular interest was that the formaldehyde-induced dose-related changes in the rate of cell replication were J-shaped with below control responses seen with the two lowest concentrations. At low concentrations of formaldehyde exposure, the incidence of nasal tumors was less than in the control group. This finding was consistent with the hypothesis that the tumor incidence risk is well predicted by the cell replication rate as was the case with the propylene oxide. The decrease in the cell proliferation rate at low concentrations of formaldehyde was proposed to be caused by a reduction of DNA synthesis and cellular replication due to the occurrence of DNA cross-links that block cellular replication complex. The number of cross-links and their rate of removal were proposed to be rate limiting, therefore controlling the replicative synthesis. While this process was still ongoing at high concentrations, the capacity of formaldehyde to form the DNA cross-links was believed to be overwhelmed by its capacity for inducing cytotoxicity, leading to the increased ~~rumor~~ response at high concentrations of exposure.

Other examples of dose-dependent changes in the metabolism of xenobiotics as affected by enzyme saturations have been shown to affect dose-dependent toxicity transitions. For example, Belinsky et al. [119] assessed the implications of saturation of bioactivation of the carcinogen nicotine-derived nitrosamine ketone (NNK) on adduct formation. NNK forms AQ13
$O^6$-methyl guanyl adducts eightfold more efficiently at low IP doses (0.3–1.0 mg/kg) than at 100 mg/kg. The difference in response between the high and low doses was hypothesized to be due to the saturation of a local enzyme that produced the methylating agent. A similar type of dose-dependent kinetic mediated response was reported for vinyl chloride. In this case, the tumor incidence response is linear at low dose but flattens out at high doses (1,000–10,000 ppm). Of interest is that testing at only high doses would have yielded an underestimation of tumor risks to the low-dose range with standard modeling procedures [116,117].

## Plotting Data: A Key Element in the Threshold versus Linearity Debate

There has been considerable debate in the toxicological literature on the plotting/graphing of dose–response relationships. This debate has been led by William Waddell of the University of Louisville, who argues that dose–responses should be plotted via the use of logarithms rather than linear scales. Waddell has argued that current risk assessment methods typically assure that there is no safe exposure to carcinogens, only at a zero dose. He claims further that the selection of linear scales for plotting dose–response relationships has no scientific basis and, in effect, has concealed the existence of thresholds. The perspective of Waddell was stimulated by Rozman et al. [120], who argue that how one plots data can affect their perspective on the nature of the dose–response. These authors asserted that the case for low-dose linearity emerged from a conversion of the logarithm plotting of the dose–response as recommended by Gaddum in 1945 [121] to an arithmetic approach but a few years later. Based on data concerning the ~~indication~~ of CYP A1 by Tritscher et al. [122], who used nearly two dozens of doses of tetra-CCD, the data plots were compared with either an arithmetic or logarithmic approach. Arithmetic plotting created the distinct impression that the measurements were taken close to zero and that the Michaelis–Menten-based fit would be approaching zero. Rozman et al. [120] indicated that the arithmetic plotting creates a profound misrepresentation of the findings. They indicated that the dose–response should be represented logarithmically since one molecule is in close proximity to a zero


ED_002751_00030366-00019

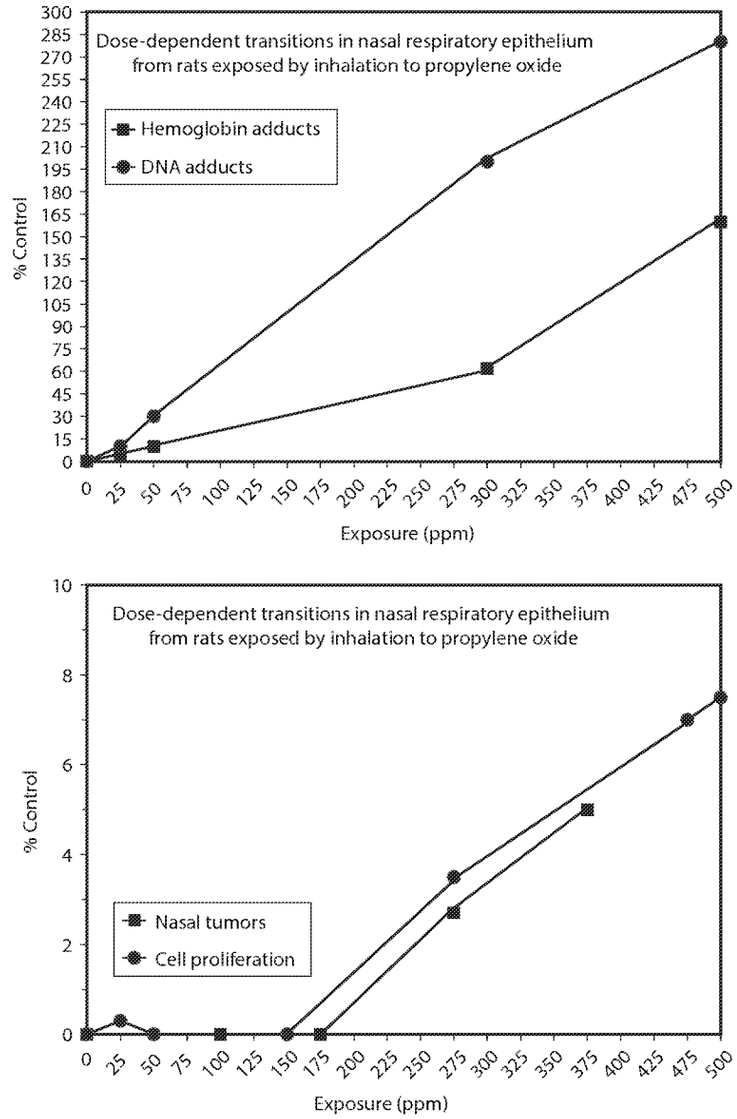



**FIGURE 3.20** Dose-dependent transitions for nasal respiratory epithelium from rats exposed by inhalation to propylene oxide. (Based on Slikker, Jr. W. et al., *Toxicol. Appl. Pharmacol.*, 201, 203, 2004; Slikker, Jr. W. et al., *Toxicol. Appl. Pharmacol.*, 201, 226, 2004.)

point of reference. A limitation to using logarithmic is that the log of zero for the control is undefined. While this is an issue, it is commonly dealt with by giving the control group a very small positive value of no practical consequence.

It is generally accepted that quantitative risk assessment (QRA) for carcinogens was implemented to replace the apparent arbitrary judgment of extrapolating animal data to humans via the use of uncertainty factors. The underlying basis for this change was via the assumption that a single molecule can cause a mutation that can cause a molecular transformation with the result eventually leading to the development of cancer. Since there was an inadequate understanding of the process of carcinogenesis and great fear of this disease, it supported a precautionary perspective. Prior to the switch to QRA for carcinogens, there was the creation of the carcinogenicity bioassay. This assay had the simple goal of answering a qualitative question: was the agent to be tested a carcinogen or not? This being the case, a large number of doses were not deemed necessary. Typically there were only one or two doses that were administered. While this testing framework was adequate to answer the qualitative yes or no question, this design failed to address the quantitative demands for assessing the cancer dose–response [120]. A qualitative test system was used by the toxicology community for critical quantitative estimates of the dose–response in the low-dose range. To further distort the low-dose evaluation estimates, the qualitative design has incorporated the maximum tolerated dose (MTD) concept (see "Maximum Tolerated Dose/Dose–Response" section) and used it as a standard.

To illustrate the difference in plotting methodology, Waddell employed data from a 4000-rat cancer bioassay with


ED_002751_00030366-00020

nitrosodiethylamine. The dose–response data strongly fit a linear dose–response relationship when plotted on the linear scale. In contrast to the linear scale, Waddell introduced the logarithmic scale [120] that plots not via the mg/kg/day method but by using molecules/kg/day. On the abscissa, a logarithm represents dose as the number of molecules/kg/day from 1 to $10^{23}$. The difference in the representation of the results is striking with the linear plotting giving the impression that the cancer risk approaches a background of zero exposure in a linear fashion. With the logarithm-scale molecule exposure model, the cancer incidence response does not approach zero molecules but approaches/collides with the abscissa at $10^{17}$ molecules/animal, thereby providing the distinct impression of a dose–response threshold.

Waddell demonstrated that this was the general pattern of dose–response relationships for numerous positive cancer bioassays [123]. The assessment of Waddell [123–134] attracted considerable attention of leading toxicologists and dose–response modelers, some of whom took issue with his methodology [135–140]. The interpretation of Waddell was disputed, dismissed as highly flawed by Crump and Clewell [135], and seen as a visual artifact based on the scale of the plot. Andersen et al. [136] stated there was no realistic representation of a threshold that could be demonstrated even in very large toxicity studies. Even though Andersen et al. were sympathetic to the likelihood of thresholds for chemical carcinogens, they argued that the only way to establish such a threshold was via a mechanistic understanding of the biological dose–response process. Lutz [137] offered further criticism of the Waddell perspective arguing that a major problem for this approach was that the logarithm transformation of the dose made it impossible to indicate a control group response since the log of 0 is undefined. He also criticized Waddell for creating this *problem* by simply subtracting the control group incidence from the treatment groups' incidence.

The series of papers of Waddell are important for a variety of reasons. The most substantial is that plotting of dose–response relationships using the number of molecules as the dose is highly instructive and provides an improved context for assessing toxicological data. Such plotting does not prevent the plotting of data via other approaches. In fact, such comparisons can lead to more insightful follow-up questions about the experimental findings. Waddell plotted tumor incidence dose–responses for 50 chemical carcinogens showing that the estimated zero response was in the $10^{17}$ molecule range/animal. This is an important observation that should not be dismissed.

An objective appraisal of this debate between Waddell and those who criticized his approach is that they came to the same practical conclusion. That is, the science reveals that there is no measureable enhanced risk at lifetime doses in which the number of molecules can reach $10^{17}$/animal even at a de minimus level. The debate over whether there is linearity existing after an extrapolation over 17 orders of magnitude of dose is simply unresolvable in a technical/experimental manner. If advocates of an LNT position can retain a theoretical belief in LNT, then it should be accompanied with the recognition that there are, at the least, practical thresholds.

The Rozman plot has been widely publicized for the assessment of carcinogens. This concept is general and could readily be applied to noncarcinogens as well. As an exercise in this regard, the number of molecules in a liter of drinking water at US EPA drinking water standards was estimated. These are exposure standards and are generally based on the reference dose (RfD)/no observed adverse effect level (NOAEL)/uncertainty factor process. That is, these exposure standards first select the most sensitive animal model, study, and endpoint, and then a threshold of toxicity is estimated. Uncertainty factors from 100 to 1000 are typically employed. At that point, a relative source contribution component is incorporated into the standard derivation process. Based on such a process, it may be expected that there should be a substantial level of confidence that an exposure of 2 L/day at the exposure standard should not be associated with any adverse health effects. That is, the exposure standards should therefore generally be considered as being of a highly precautionary nature. Yet, even with those *highly precautionary* daily exposures at the level of the drinking water standard, the number of molecules per liter is generally in the $10^{16}$–$10^{18}$ molecules/L. Once again at a rate of 2 L/day for 70 days, the number of *toxic* molecules that can be safely consumed in a lifetime from drinking water alone would be in the $10^{20}$–$10^{22}$ range. It should be noted that these exposure standards are based on the premise of protecting those at increased risk.

So what does this dose–response relationship based on molecules mean? The findings indicate that no demonstrable toxicological activity occurs until massive numbers of toxic molecules/day to noncarcinogens are administered. This is also the case for carcinogens as well.

## CHALLENGES TO THE THRESHOLD MODEL

### Introduction

The threshold dose–response has been the dominant dose–response model in pharmacology and toxicology throughout the twentieth century to the present. As discussed earlier, the biphasic dose–response model and the threshold dose–response models were advocated by homeopathy and traditional medicine, respectively, in the early decades of the twentieth century. By 1930, the biphasic dose–response, along with homeopathy, was significantly marginalized, whereas the threshold dose–response, along with traditional medicine, was transformingly dominant in the United States. In fact, the success of traditional medicine in the United States was due principally to major institutional, governmental, and performance reforms that were direct offshoots of the 1910 Flexner Report [66], transforming US medicine education into a far more scientific and rigorous profession, with a strong research base [67]. This remaking of American medical education proved to be the key vehicle for the transcendent dominance of American medicine in the twentieth century and as an offshoot, the dominance of the threshold


ED_002751_00030366-00021

model, and an offspring of traditional medicine. This critical association of the threshold model to the field of traditional medicine was the most significant factor affecting the acceptance and widespread use of this dose–response model in society. Despite its widespread acceptance and profound influence in the medical and scientific domains, the threshold dose–response model has also been the object of considerable criticism and challenged on multiple scientific and policy fronts. The following section presents and assesses the most significant challenges to the threshold dose–response model and their scientific foundations and places the threshold model and alternatives in a broad and integrative toxicological context.

### Challenge #1: LNT and Ionizing Radiation

The radiation geneticist Hermann J. Muller [88], at the University of Texas at Austin, Texas, reported that high doses of x-rays induced mutations in the germ cells of male fruit flies. Based on limited experimental data, all of it at very high doses, and some of it contradictory to his hypothesis [9], Muller soon developed a strong belief that the mutation rate would be proportional to the dose of energy adsorbed. This implied that in the case of mutation, there would be no threshold. This issue would become progressively more contentious, especially with the expanding use of medical x-rays, the development of atomic weapons, dropping of the atomic bomb, and testing following their atmospheric explosions in the early cold war years.

During the 1920s to the early 1940s, the use of x-rays for therapeutic purposes for children and adults was extensive, treating arthritis, sinus infections, staphylococcal infections, otitis media, tuberculosis, pneumonia, and a myriad of other conditions besides cancers [46]. Seen within this perspective, one could sense the value of health concerns expressed by Muller, even if he might be incorrect with respect to the linearity hypothesis. It was only following the commercialization of penicillin after WWII and the rapid development of other antibiotics that the use of x-rays for such conditions was abandoned.

With respect to ionizing radiation, the idea of a threshold dose–response was first proposed in the mid-1920s based on occupational exposure concerns. The threshold concept was associated with the idea that workers could tolerate a certain amount of exposure without any significant health concern. AQ14 That the threshold would need to be exceeded before harm would occur was generally accepted and especially accepted by the medical community. However, this view would become challenged by Muller following his discovery that x-rays induced mutations in fruit fly germ cells.

The first national impact of Muller's findings and advocacy occurred in 1935 within the American X-ray and Radium Protection Committee, later (1946) to be called the National Committee on Radiation Protection and Measurement (NCRPM). At this time, an unnamed committee member wrote to Taylor with the recommendation that the tolerance dose be reduced from 0.1 to 0.05 R/day based on the Muller findings that suggested a cumulative effect of x-rays on the genome over a prolonged period of time. Yet, the committee was at a loss as to how to extrapolate the findings in fruit flies to humans and to do so in a quantitative manner. Nonetheless, the data of Muller and others were kept at the forefront as the committee struggled with the issue of reproductive safety within the workplace and for patients. Over the next several years, the minutes of this committee reflect how the findings of Muller progressively came to challenge the view of a threshold. At the December 1938 meeting of the committee, a proposal was offered to amend the statement on the tolerance dose to the following: "The generally accepted tolerance dosage is taken as $10^{-5}$ r/sec for a 7 hr day. Geneticists on the committee pointed out that because of the cumulative effect of X-rays the tolerance dose should not exceed $10^{-6}$ r/sec ([82], see footnote 300)." By the December 1940 meeting, the committee explicitly stated that the rationale for lowering the tolerance dose was because of a concern with mutational effects ([82], see footnote 305). This recommendation did not sit well with the influential Failla who felt that a switch to a mutational endpoint would create considerable uncertainty since there may not be a threshold for a genetic effect. However, the data were still not viewed by the majority of committee members as adequate to prove that a threshold did not exist.

The committee tried to find a way through the confusing dilemma of the threshold versus linearity debate. While the committee believed that the term tolerance dose referred to a dose that could be tolerated or accommodated without any biologically significant damage, this was not the case with genetic damage that was thought to be irreversible, cumulative, and harmful. The dose–response change from threshold to linearity would lead to a new concept called *permissible exposure*. This was an important change because a permissible dose could still injure; it was not considered *safe*.

Permissible exposure was the means by which the *acceptable* risk concept became operational. Whether the general public understood or misunderstood the differences between a tolerance dose and a permissible dose is not known. Nonetheless, it would have important implications for the process of risk assessment and risk management. In offering a compromised position, the committee proposed not changing the exposure standard (i.e., a practical solution); this would placate the supporters of threshold; however, they would yield on the theory. The dose–response concept would change from a tolerance phenomenon based on the threshold concept to one without a threshold. The exposure would now be seen as a permissible dose, a concept built upon *acceptable risk*. The permissible dose terminology therefore represented a profound conceptual change, indicating that a threshold for x-ray-induced germ cell mutations was no longer assumed. However, despite the years of debate and the switch in terminology and concept, this critical policy change was never published (i.e., acted formally on); this failure to follow through on the agreed course of action would lead to new controversy and debate in the years immediately following WWII.


ED_002751_00030366-00022

The permissible dose concept was not lost during WWII despite the inactivity of the committee during that period, as committee members were reassigned to other activities for the duration of the war. However, following the end of the war and with the Nobel Prize recently received (i.e., December 1946), Muller was invited to join the NCRPM that was chaired by the more conservative Failla. In their 1947 draft report, the committee dropped the tolerance dose concept since ionizing radiation was now assumed to have no threshold and to display cumulative damage. Once again, organizational inertia and personal disputes hit and the 1948 recommended changes of the NCRPM would not be published for some 6 years! Based on these factors, it was hard to predict the behavior of the NCRPM committee. However, its actions were quickly overshadowed by a new NAS/NRC committee that was dominated by Muller and other radiation geneticists that were loyal to his perspective. The situation was also problematic since some scientists, such as Muller, with clear ideological perspectives, were serving on multiple national and international advisory committees, addressing the same dose–response policy topics [9].

In their groundbreaking publication of 1956, the NAS Biological Effects of Atomic Radiation (BEAR I) committee [141] formally asserted the concept of low-dose linearity for ionizing radiation-induced germ cell mutation. The geneticist community, as lead by Muller, saw the NAS committee as the vehicle to finally change the national risk assessment policy and to do so in a highly visible and far-reaching manner. That is, the 1956 report was widely distributed, was the subject of considerable media attention, and would have a profound impact on policy. The genetics section was intentionally written to be read by a general reader, further enhancing the spread of the linearity concept and fear of radiation in the media and general public.

The transition from threshold to linearity required about three decades, starting with Muller's seminal publication in 1927 [88]. During an oral history, the longtime chairman of the NCRPM Lauriston Taylor revealed that his committee was awaiting anxiously for the guidance of the prestigious NAS committee as they wanted to follow its lead. Within 1 year of the 1956 NAS report, the NCRPM generalized the concept of linearity for germ cell mutation to somatic cells, thereby affecting cancer risk assessment [9]. Soon other national and international committees would concur and a remarkable dose–response revolution had occurred, with significant long-term implications and consequences.

The generalization from the germ cell linearity response to somatic cell linearity was a key event, especially coming so soon after the NAS BEAR I report. It was also remarkable because even though the NAS BEAR I committee carried the greatest scientific credibility, the NCRPM committee, in effect, affected the major policy change. It is ironic that the NCRPM committee, which so intensely and anxiously awaited the guidance of the BEAR I committee, actually ignored guidance that emerged from the BEAR I committee activities on the question of somatic cell effects. More specifically, in a reading of the near-final draft report of the genetics panel of the BEAR I committee, Dr. Warren Weaver, chairman of that committee, stated on February 5, 1956, that "A little radiation, now and then, does not directly harm the person receiving it." Weaver then quoted from the next paragraph of the same report:

> From the above statements a very important conclusion results. Although there may be and probably is, a safe rate at which a person can receive radiation (say so much per week) if one is concerned only with direct damage to that person, the concept of safe rate of radiation simply does not make sense if one is concerned with genetic damage to future generations.

In the final report of the 1956 BEAR I committee, one can see a generally similar but slightly nuanced restatement of the earlier drafted statement as quoted by Chairman Weaver. The final report states:

> It has sometimes been thought that there may be a rate (say so much per week) at which a person can receive radiation with a reasonable safety as regards certain types of direct damage to his own person. But the concept of a safe rate of radiation simply does not make sense if one is concerned with genetic damage to future generations.

Both the near-final draft and final report statements are in agreement on the genetic effects to future generations. As for the somatic cell effects, the draft report is clear that a threshold effect is emphasized. The final report restates the somatic cell threshold interpretation but more subtly via a type of third-person comment rather than the more direct style of the draft report. Nonetheless, the NCRPM made the leap to linearity for somatic effects, not the genetics panel of the 1956 BEAR I NAS committee.

The generalizing of mutation linearity dose–response to somatic cells and its impact on cancer risk assessment was profoundly influenced by one of Muller's geneticist colleagues and future Nobel Prize winner, E.B. Lewis, and fueled by his widely acclaimed article in the journal *Science* [142] along with an accompanying and highly supportive editorial by the journal's editor in chief [143]. Muller likewise had obtained prepublication copy of the Lewis *Science* paper and distributed it to key groups such as the NAS BEAR genetics panel in December 1956, emphasizing the estimated cancer risk to the human population from radioactive fallout [82]. Thus, the first serious challenge to the threshold dose–response model was one of a developmental scientific perspective that was set within a highly charged international political context.

While the 1956 BEAR committee did not formally address the issue of somatic effects, the 1960 BEAR committee did. The conclusion of this committee on this issue is given in the following quote from its final report. The committee stated that it "does not consider it justifiable to predict human tumor incidence from small radiation doses based on extrapolation from the observed incidences following high dosage." Furthermore, the 1960 BEAR committee acknowledged that the number of mutations in mouse sperm and oogonia was


ED_002751_00030366-00023

less when the x-rays were given at a lower dose rate than with an acute exposure in which the dose rate was greater but the total dose was identical under both approaches. This was a conclusion of the Caspari and Stern [144] study with *Drosophila* sperm that caused so much scientific confusion and subterfuge by Stern and Muller as they desperately tried to deflect the findings of the Caspari research [10,29,39,145]. Now some 12 years later, the findings were generalized to mice based on the work of William Russell at Oak Ridge. At his Nobel speech, Muller would argue that similar damage with the same cumulative dose, despite different dose rates, was de facto proof of the linearity model. Yet now, he would make no such statement in the context of the 1960 BEAR committee. Nor would the BEAR committee of 1960 and its genetic panel, still dominated by Muller, change their linearity recommendation for mutational effects in light of the challenging findings in mammalian cells to the linearity dose model.

These historical quotations are not simply the stuff of academic arguments but should be seen for how they came to impact major public policy in the dose–response and risk assessment domains [29]. The NCRPM gave the impression of deferring their position to that of the 1956 BEAR I committee; yet they developed a policy on somatic cells that was not formally addressed by this NAS/BEAR I committee in a direct policy sense but was actually in apparent conceptual disagreement with it. Furthermore, a position on somatic cell responses for cancer was explicitly addressed by the prestigious 1960 BEAR committee; it did not support the concept of extrapolating from high to low doses for cancer risk. This position was in direct conflict with the recommendations of the NCRPM. However, it was the 1956 report of the NAS BEAR I committee that received enormous publicity within the scientific community and the popular press, while the 1960 NAS BEAR committee's report was generally overlooked, lacking any notable impact. This point was explicitly addressed by a member of both committees, Dr. James Crow [146] and others (e.g., [147]), in a subsequent historical evaluation of the impact of such National Academy of Sciences efforts on radiation health policies in the United States.

While the 1956 NAS committee and other influential advisory committees were adopting the LNT perspective, an important independent action in the US Congress was about to come to a similar conclusion, also with profound implications. That is, the Delaney *Amendment* to the Food Additives Amendment became law on April 26, 1958. It affirmed that no additive would be considered if it induced cancer in animal models or humans. The Delaney Clause was subsequently placed into the Color Additives Amendment of 1960 in response to the highly publicized cranberry crisis of 1959 [148].

The Delaney Amendment was premised on a belief in linearity at low dose for chemical carcinogens. Over time, the FDA would modify the Delaney Clause to address the issue of de minimus risks, that is, a risk that is both too low to be accurately measured and below practical concern. This modification enabled FDA to permit carcinogens to be added to food if the estimated risk had lower than a calculated risk (e.g., $\leq 10^6$/70 year lifetime) deemed to be de minimus, based on animal extrapolation and biostatistical modeling procedures. Despite their similarity in time, the development of the LNT cancer risk assessment model in the Delaney Clause developed independently of the NAS BEAR I-inspired LNT cancer risk assessment activities, although their implications converged [9].

The next serious challenge of the LNT model to the threshold dose–response model occurred two decades later in 1977 in the bursting forth of the environmental regulatory revolution in the United States when the NAS Safe Drinking Water Committee (SDWC) recommended that the EPA ~~applies~~ the guidance of the NAS BEIR II committee for ionizing radiation to the domain of chemical carcinogens [149]. From the late 1950s to the early 1970s, profound intellectual debate focused on the linearity versus threshold policy decision for ionizing radiation and cancer risk. As noted, the NCRPM first recommended the switch from threshold to linearity. In fact, the NCRPM orchestrated a very significant compromise between the opposing parties of this debate [8]. It got the linearity advocates to admit that the data supporting linearity at low dose were not convincing. Likewise, the same argument was used against the threshold perspective. As a result of this intellectual impasse/conundrum, the committee concluded that

> it was not possible to establish the exact character of the dose curve. Lacking sufficient unequivocal information, the committee believed it would be desirable to take a conservative position and to assume a non-threshold linearity dose response relationship.

While this position seemed to represent a compromise, it represented a major victory for the concept of the *precautionary principle*. This was similar to the type of compromise that was brokered in the 1940s over the issue of tolerable dose versus permissible dose. However, in that earlier case, the outcome was far different. The concept of permissible dose was accepted as scientifically more plausible, but the threshold concept would govern the regulation. Some 25 years later, the concept of linearity had lost scientific support, yet its underlying philosophical perspective (i.e., precautionary principle) was adopted by the NCRPM. Other leading advisory groups would also struggle with this problem with the NAS BEAR committee of 1960 rejecting linearity on scientific grounds, whereas the US FRC (1960) accepted the linearity concept based on the precautionary principle. This type of back-and-forth struggle would continue between different committees and their varying compositions over the next decade. However, the precautionary perspective reemerged with the next NAS committee (now called BEIR I/II, 1972) [149], a perspective that would strongly affect the actions of the 1977 NAS SDWC [150]. This committee would also rely heavily upon a series of papers they claimed that supported the scientific foundations of low-dose linearity [151–154]. AQ15

The EPA accepted this 1977 recommendation of the SDWC and, within 2 years, applied the LNT model to the


ED_002751_00030366-00024

risk assessment of trihalomethanes (THMs) and then soon to dozens of other chemical carcinogens up to the present. The theoretical foundation of this challenge to the threshold dose–response model for chemical carcinogens was built upon eight guiding principles as laid out in the NAS book *Drinking Water and Health* [150]. The eight principles are as follows:

1. Only one or two changes in a cell could transform it, and this could lead to cancer.
2. Human population heterogeneity was a factor, and some people may be at greater risk. Such heterogeneity leads to the conclusion that there was no population-based threshold.
3. A transformed cell will be irreversibly propagated.
4. If the mechanism involved mutation, there would be no threshold; in fact, if there were no information on mechanism and cancer occurred, mutation should be assumed.
5. It is necessary to assume that a single molecule or a few molecules can cause a mutation. Therefore, linearity at low dose can be assumed.
6. There is also the assumption that the response would be directly additive to background, if acting via the same mechanism. This would also support the linearity conclusion.
7. Available mutagenicity data with radiation indicated that it was linear at relatively *low* doses.
8. Since chemical carcinogens act like ionizing radiation, low-dose linearity should also be assumed to be the case for such chemicals.

It is also evident that the committee did not choose to document possible alternative opposing arguments to linearity at low dose or weaknesses in the so-called eight principles. Furthermore, it would have been of considerable value if the committee had ranked the principles in terms of the degree of scientific confidence that each had individually and its relativity to each other. The committee should have distinguished those principles that were guided by scientific data as compared to those more influenced by a protectionist philosophy rather than science. Furthermore, these key references used by the 1977 SDWC provided data and/or conclusions that directly contradicted the previous principles #1, #3, #4, and #5. For example, Nordling [154], Muller [152], and Iversen and Arley [153] argued that multiple successive mutations in the same cell (i.e., up to seven mutations) would be needed to cause human cancer, thereby challenging key principles of 1977 committee that relied upon these papers.

While each of the eight guiding principles was important in order to provide the underlying support for the EPA to adopt low-dose linearity for carcinogen risk assessment, the intervening four decades have not provided confirmatory support for any of these *principles*. Rather, the findings that have emerged during this time period have, in fact, revealed that those views are now generally either scientifically untenable or practically impossible to study at a sufficient level of detection. For example, that a single alternation in DNA would be sufficient to lead to cancer or that the process of carcinogenesis, once initiated, is irreversible has been repeatedly demonstrated as not occurring [111]. Driver et al. [155] demonstrated a strong linear dose–response relationship from DMN-induced adducts and foci production in the kidney of male F344 rats. However, the linear dose–response pattern disappears displaying clear evidence of a threshold dose–response for this genotoxic carcinogen (Figure 3.21). Such a dose–time response strategy supported the concept of cancer being a multistage process and with repair-related processes occurring at lower doses, resulting in a regression or suppression of the carcinogenic process.

The idea that chemically induced cancer occurs via the same mechanism as similar as background cancer in the population has not been established. The level of mechanistic detail and biological complexity today reveals how superficial and implausible the *principle* was. In fact, in the domain of x-ray-induced germ cell mutation in fruit flies, it was shown that low dose of x-rays induced a DNA repair process that repairs background lesions while having no effect on those mutations induced by the x-rays [156]. The additivity to background concept would fail in this case as well. Thus, the concept of *reasonable* guiding principles became confused to mean something akin to scientific certainty. The confusion was not only passed on the general public but has affected the development of regulatory agencies' risk assessment actions for chemicals and ionizing radiation with widespread societal implications.

## Challenge #2: Hormesis

### Historical Foundations

The challenge to the threshold and LNT dose–response models from the hormesis dose–response is relatively recent, being little more than a quarter century old. While the concept of hormesis is about 130 years old, starting with the German physician and pharmacology/toxicology professor Hugo Schulz in the 1880s, that it might challenge current models or might inform the risk assessment process was probably first suggested by Donald Luckey et al. in 1975 [157] in the introduction of the book *Heavy Metal Toxicity, Safety and Hormology*:

> Agents which are found to cause stimulation when given in small quantities are colled [called] *hormetics* and the action is *hormesis*, taken from Southam et. al. [and ~~Erhlich~~] (1943). AQ16
> Unterstanding [Understandings] the extent of this phenomenon is essential before world wide committees and legislative bodies make recommendations which consider only toxic actions…

This publication was followed 5 years later by a detailed book by Luckey [53] on ionizing radiation and hormesis that raised the visibility of this concept within a new scientific regulatory context. While the issue of hormesis or biphasic dose/responses seen in an earlier era in the confrontation between homeopathy and traditional medicine was in the


ED_002751_00030366-00025

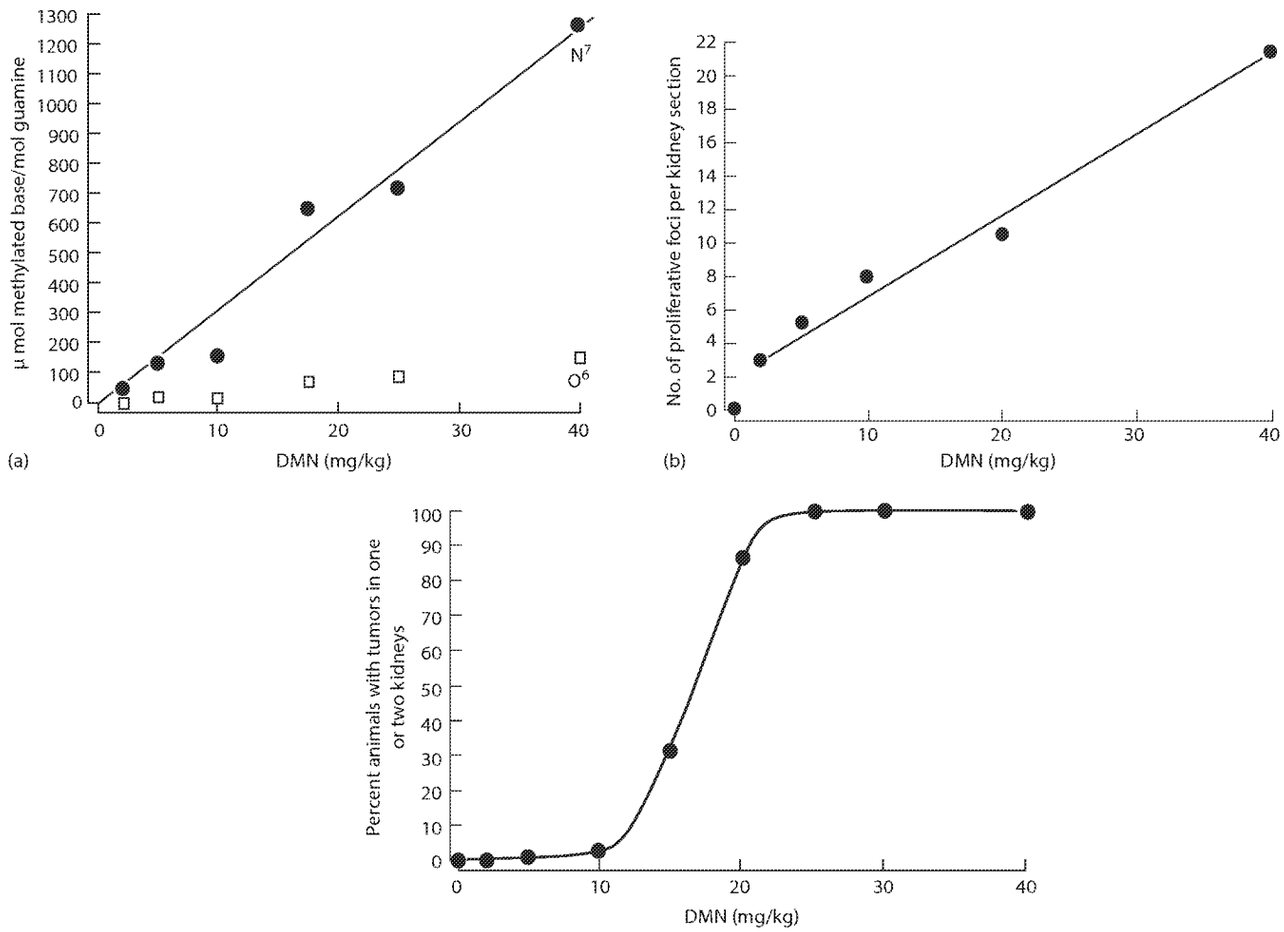



**FIGURE 3.21** Dose–response for DMN: (a) renal adducts, (b) renal foci, (c) renal tumors. (From Driver, H.E. et al., *Br. J. Exp. Pathol.*, 68(2), 133, 1987.)

attempted commercialization of treatments to enhance agricultural production [4], the goals of Luckey were different. He was far more academically based, with the ostensible goal to educate the regulatory community to the scientific foundations of the hormesis concept and its regulatory implications for setting exposure standards in all types of settings, be they occupational, environmental, food, or consumer products, within the home for concerns such as with radon gas. While these initial activities of Luckey created interest in the hormesis dose–response model, they were not persuasive to the regulatory communities and lead to frustration in dealing with agencies such as EPA in the regulation of carcinogens—especially for ionizing radiation as reflected in a number of his subsequent publications.

Despite the 1980 book by Luckey, the dose–response debate during the early 1980s was not focused upon hormesis versus LNT per se but threshold versus LNT. In fact, this still is the case, even today, all for practical reasons. The regulated industry in both the chemical and radiation areas supported the less conservative threshold dose–response model, whereas the EPA had established the LNT model for their estimates of risks from carcinogens. Using the LNT model in the risk assessment process and in guiding risk management decisions was proving to be very costly to the industry. A key goal of the regulated industry was to find a means to convince the EPA to switch back to the threshold dose–response model for risk assessment purposes. A practical problem for the industry was that the agency assessed each chemical in the chronic bioassay (i.e., the 2-year rodent bioassay) on its own merits, evaluating whether the data generated in the bioassay best fit a linear or threshold model. While this might seem to be an objective approach, there were too few doses to objectively differentiate which model best fit the data. The very few doses were also delivered at very high dose rates, that is, at the maximum tolerated dose (i.e., the highest dosage that would not cause frank toxicity and not reduce body weight by more than 10%) and one-half of that value. With so few doses and those that were used being delivered at such a high dose rate, there were high-dose toxicological concerns and biostatistical limitations that could not be overcome. For all the attempts to rationalize the adequacy of those standard types of bioassay studies, they were far from perfect and not adequate to provide the type of data needed for risk assessment purposes for low-level exposures.


ED_002751_00030366-00026

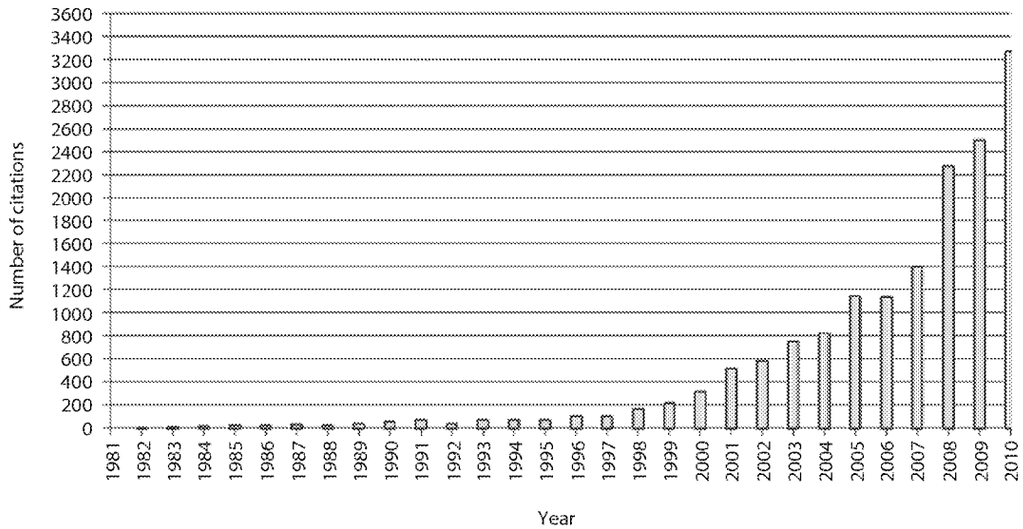



**FIGURE 3.22** Citations of hormesis/hormetic in Web of Science database.

Typically both a linear model and a threshold model could similarly account for the observations that are produced in the chronic rodent bioassay. Since one biostatistical model is not particularly superior to the other for data generated in their experiments, the EPA, in such cases, invariably defaults to the most conservative or protective dose–response model. Thus, the linear model became the model selected, by default. There was no practical way around this risk assessment dilemma. The rules of the risk assessment process were very strongly biased toward using the LNT model. Thus, many in industry felt that the government's guidance rules were not scientific and were designed to always yield the same conclusion.... Thus, the *scientific* deck seemed to be stacked to yield a predetermined result.

Since the threshold model could not practically account for dose–response data better than the LNT model for the standard chronic bioassay data, some groups in the industrial sector became interested in the hormetic dose–response (HDR) as it might be easier to distinguish it (i.e., the HDR model) from the LNT than the threshold dose–response model. This might provide a better opportunity to avoid risk assessment estimates based on linearity. Secondly, the hormesis model had a threshold component and it was the establishment of a threshold that was the real goal. The fact that the hormesis model had the potential to estimate a possible public health benefit was politically problematic for industry since it would not be a wise strategy to claim that pollutants could induce beneficial effects at low doses, even if true. This can be readily seen in the range of policy concerns directed at the hormesis concept [158–161]. As stated previously, the goal of the industrial supporters of hormesis is for the threshold concept to gain regulatory traction, not for the concept of health benefit to be the focus.

The electrical power industry from the United States and Japan explored the area of hormesis by conducting a conference in August 1985 with the peer-reviewed proceedings published in the journal *Health Physics* in 1987. The proceedings were followed 2 years later by a debate on the issue of radiation hormesis in the journal *Science* by leaders of that initial conference [162,163]. While the issue of hormesis had resurfaced during the 1980s, it was a modest initial revival as reflected by citations in the Web of Science, which averaged only about 10–15/year (Figure 3.22).

### Biphasic Dose–Responses: Multidisciplinary

Despite the rather slow unfolding of the scientific rediscovery of the hormesis concept during the 1980s, there were other developments that suggested an intellectual convergence on the topic of biphasic dose–responses. None of these newer developments were directly related to policies or specific actions of regulatory agencies. Reports from multiple scientific fields began to independently appear on the occurrence of hormetic-like biphasic dose–response relationships. For example, a significant development in the field of pharmacology occurred with the highly influential papers by Szabadi [164,165], which summarized the occurrence of biphasic dose–responses as far back as 1906, starting with research of the 1936 Noble Prize winner Henry Dale (1875–1968) [166] (see "Challenge #3: Pharmacology and the Biphasic Dose–Response" section). Of particular importance was that Szabadi [165] proposed a receptor-based mechanistic model by which such biphasic dose–responses could occur. The Szabadi [165] paper generated a spate of supportive commentaries and related papers [167–171], providing a strong foundation for further developments in this area. Likewise, the field of epidemiology published a number of studies showing U-shaped dose–responses for various types of medical and public health outcomes associated with environmental and occupational exposures [172]. A series of papers were published by Stebbing [173–175], providing a strong


ED_002751_00030366-00027

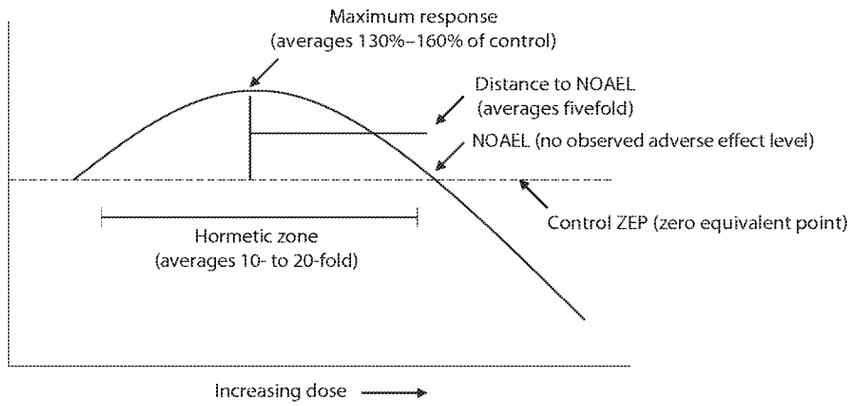



**FIGURE 3.23** Dose–response curve depicting the quantitative feature of hormesis. (Based on Calabrese, E.J., *Am. J. Pharmacol. Toxicol.*, 3(1), 56, 2008.)

complement to the writings of Luckey concerning environmental toxicants and HDRs. During this period, researchers in the area of genetic toxicology reported that low doses of chemical mutagens could induce DNA repair processes that would provide protection against subsequently more massive exposures to the same or different mutagenic agents [176]. By 1984, the concept of adaptive response to ionizing radiation had been reported by Shelly Wolff at the University of California at San Francisco [177]. In 1986, the concept of preconditioning in the biomedical sciences was published, which demonstrated that a short-term/low-dose prior hypoxic exposure would protect against a massive myocardial infarction-induced cardiac damage by about 70%–80% [178]. The findings from each of the previous cited areas of adaptive responses were soon replicated in extensive studies and then generalized to other cell types, organs, and biological models. The shape of the dose–response in each of these general areas was consistent with that of the HDR. In parallel with these emerging findings was the rapid development of in vitro methods and extensive economic and political pressure to employ fewer whole animals in biomedical and toxicological research. The switch to in vitro methods created the opportunity to assess more doses/concentrations per experiment. These changes have profoundly affected the conduct of toxicology, creating the opportunity to routinely evaluate from 8 to 10 doses per chemical screening. In fact, it was as a result of the newly acquired change to in vitro testing and its high-throughput dimension that profoundly expanded the number of reported cases of HDRs in the biomedical literature. The reliance upon test results with doses at the MTD and fractions of the MTD would not have the potential to explore the biological effects of low doses, including the hormesis hypothesis.

### Hormesis Database

The 1980s therefore set the toxicological and biomedical stages for the evaluation of the HDR. The 1990s and the first decade of the new millennium witnessed a large increase in the reporting of HDRs in the toxicological and biomedical literature. This increase is especially evident in the second half of the 1990s. The hormetic response was found to be quite common, as well as very general, being independent of biological model, endpoint, and inducing agent. The HDR was also shown to display specific quantitative features, that is, the low-dose stimulatory response was generally quite modest with the maximum response being typically only about 30%–60% greater than a concurrent control group (Figure 3.23) [179–181]. This modest response would present challenges for the observation of hormetic responses, in attempts to distinguish it from normal background variation. Proving the occurrence of an HDR requires greater sample size/statistical power in the low-dose zone along with careful consideration of dose selection with more doses below the threshold along with a heightened need to replicate findings. Given the modest nature of the low-dose stimulation, it is essential that more detailed understanding of the historical variation in the control is known. Thus, false-positive low-dose stimulations could occur as a result of low-control group readings due to normal variation. This has also led to the need to conduct statistical simulations in order to estimate the frequency of false-positive responses. As a result of the recognition of such methodological challenges that are inherent in the assessment of HDRs, it has resulted in adding more dose–response insights, affecting the quality control, experimental design, and response criteria, thereby making conclusions concerning the likely presence or absence of HDRs more reliable. This is especially seen in the prospective testing of specific HDR hypotheses that are becoming more common in the biomedical and toxicological literature.

### Defining Hormesis

As a result of the renewal of interest in the hormesis concept in the early 1980s, at least in part, via an industry initiative to avoid an LNT-driven regulatory-based cancer risk assessment, the low-dose stimulatory part of the HDR became viewed by some as beneficial. Without adequate evaluation, some in the environmental regulatory community became either suspicious or opposed to the HDR for philosophical/


ED_002751_00030366-00028

ideological reasons rather than scientific. However, the low-dose stimulatory aspect of the HDR is neither inherently beneficial nor harmful [182–185]. One needs to assess not only the data from the experiment but also the biological context of the findings in order to make an informed judgment concerning whether the low-dose stimulation is potentially beneficial, harmful, or neither. When the low-dose stimulating results in enhancing longevity, greater disease resistance, improved memory, greater bone strength, and other comparable apparently desirable responses, it has generally been viewed as *beneficial*. When the responses reflect the enlargement of the prostate gland, the enhanced proliferation of tumor cells, or other undesirable responses, it has been viewed as potentially harmful [182]. In many cases, the clinical or public health implications of a low-dose stimulation may not be large enough to be practically significant. In such a case, the clinical or societal implications may be/are uncertain. Thus, the HDR is a scientific concept—not an ideological element.

Many in the endocrine disruption area describe such biphasic dose–responses as U-shaped nonmonotonic dose–response—not an HDR [184]. Yet, the quantitative features of the biphasic endocrine disruption dose–response follow similar quantitative features as that for the HDR. The underlying molecular mechanisms also follow similar receptor-based and signaling pathway-based processes. It is the opinion expressed here that the inverted U-shaped dose–responses reported within the context of endocrine disruptive agents are generally manifestations of the HDR model of hormetic response–endocrine disruption. The issue over terminology and language is important, especially in order to assist researchers, governmental officials, and others to better understand and apply the dose–response concept.

### Hormesis Frequency

While the 1990s and early 2000s witnessed the publication of a large number of HDRs being reported in the biomedical and toxicological literature, there emerged the question of what was the frequency of hormesis in toxicology and pharmacology. Using rigorous entry and evaluative criteria, this question was assessed based on a review of approximately 21,000 papers from the toxicological, biomedical, and life sciences areas. It yielded a value approaching 40% for the frequency estimate of hormetic responses that satisfy rigorous a priori entry and evaluative criteria [186–190]. This observation was supported in follow-up large-scale evaluations [191–193].

Such results were striking since they represented a significant conceptual transition in the toxicological literature. That is, when the hormesis concept was beginning to be discussed in the 1980s, it was uncertain whether it was a real and reproducible phenomenon. If it was, then it was thought that it may be uncommon, rather infrequent, a type of paradoxical phenomenon. Yet, the deeper the investigations probed, the more general and frequent this dose–response was found to be.

### Validation of Dose–Response Models

In the course of the previous evaluations of the HDR, the question was raised as to how the toxicology and pharmacology communities had validated the threshold dose–response model during the twentieth century. Since so many of environmental and occupational health regulations and FDA exposure standards were based on the use of the threshold dose–response model, it seemed logical to assume that these agencies as well as the scientific community must have validated the capacity of the threshold dose–response model to make accurate predications in the below-threshold zone. However, follow-up detailed searches of the literature did not yield any published attempts to test the validity of the threshold dose–response model predictions in the below-threshold zone. Likewise, interviews/discussions with senior toxicologists, both within and outside of government, also did not yield any published attempts that validated the low-dose prediction of the threshold dose–response. The below-threshold zone is critical since this is the area of the dose–response where humans principally live. While it is not possible to prove a negative, the results of multiple detailed searches of the literature to obtain articles that validated (or attempted to validate) the threshold dose–response model have been without success. This search failure has led to a tentative but confident conclusion that the toxicology, pharmacology, and regulatory communities failed to validate (or attempt to validate) the threshold dose–response model for accurate predictions in the below-threshold zone during the entire twentieth century.

When the concept of validation was then applied to the three most dominant dose–response models (i.e., threshold, LNT, and hormetic), using multiple, independent large data sets, the only one that was effective in accurately predicting responses in the low-dose zone was the HDR. The threshold model revealed that this model consistently failed to accurately predict responses across the entire spectrum of agents tested [193]. Inaccurate predictions were even more common for the LNT model. These observations were as challenging as they were surprising. These tests to validate the dose–response models upon which regulatory programs have been based were performed only long after these models had been adopted and applied by regulatory agencies in many countries. Thus, multiple decades after their establishment and acceptance, critical inadequacies were uncovered for key risk assessment dose–response models used for most risk-based regulations. Yet, enormous regulatory, administrative, and legal decisions have been made based on these dose–response models that were assumed by the public, elected officials, and probably the scientific community to have been vetted and validated by the scientific and regulatory communities.

The need to validate the capacity of dose–response models to make accurate response predictions, especially in the low-dose zone, is a surprisingly new development to the fields of toxicology, pharmacology, and risk assessment. It is a highly significant practical problem at present in these respective fields because the threshold dose–response model


ED_002751_00030366-00029

was adopted nearly a century ago presumably on the assumption that it could make accurate estimates of responses below the threshold independent of biological model, endpoint, and chemical agent. The model estimates are supposed to be reliable and to provide confidence to the public that exposure standards are based on accurate dose–response estimates. The question must therefore be raised as to why the threshold dose–response model was accepted for regulatory use without having been evaluated. In fact, the model was accepted even in the absence of any documentation of what would be an acceptable model and how that decision would be made.

Beyond questions concerning what is an acceptable dose–response model for risk assessment purposes, the acceptance of a model has other important implications that may be overlooked. From a historical perspective, once the threshold dose–response model was adopted and integrated within governmental regulatory frameworks, a hazard assessment process was created based on the assumption that the threshold dose–response model provided accurate estimates of responses below the threshold. This hazard assessment testing protocol determined how chemicals would be tested and evaluated, including the animal models selected, the number and the spacing of doses, and the dose selection strategy. In fact, as a result of accepting the threshold dose–response as the model to be used in the estimation of responses in the low-dose zone, toxicology would become a discipline that would be characterized as using only a few very high doses in the chronic bioassay.

The hazard assessment concept was built upon several data requirements and goals: first, demonstrate toxicity at the highest dose while not exceeding the maximal tolerable dose; secondly, it is important that no statistically significant increase in toxicity occurs at the lowest dose so that a threshold dose might be more readily demonstrated. There was no interest in obtaining information on the entire dose–response continuum as it was assumed that only random bounce or noise would be observed for responses to doses below an estimated threshold. This type of hazard assessment methodology reinforced the assumption that the HDR did not exist. It was on this basis that past toxicological assessments were based.

There are multiple flaws in this hazard assessment process. If the high dose was too high, then the study would be dependent upon only a single dose. Since the second dose was still 50% of the high dose, this was also at risk for exceeding the MTD. Regardless of whether both doses provided valid data concern would still remain over what was the response at lower doses and whether the threshold was reasonably well characterized for the most sensitive endpoint. All the assumptions that were built into the bioassay and how the data that it produced would be interpreted were derived from assumptions about the threshold dose–response model. Nonetheless, the acceptance of the threshold dose–response model does not excuse the several decades of using only two doses before switching over to three. Even in the case of three doses, each separated by a factor of two is still far from satisfactory for estimating responses in the zone approaching a possible threshold as well as below the threshold.

The background tumor/disease incidence could affect the selection of the animal model. In the case of the HDR model, it would be necessary to test the predictive capacity of the model by ensuring that the control endpoint incidence for tumors and other disease endpoints would be such that one could detect a decrease in the incidence if hormesis were present. If the background incidence is negligible, then it would be impossible to detect the presence or absence of the HDR. The background disease incidence was not of theoretical concern in the selection of the threshold model.

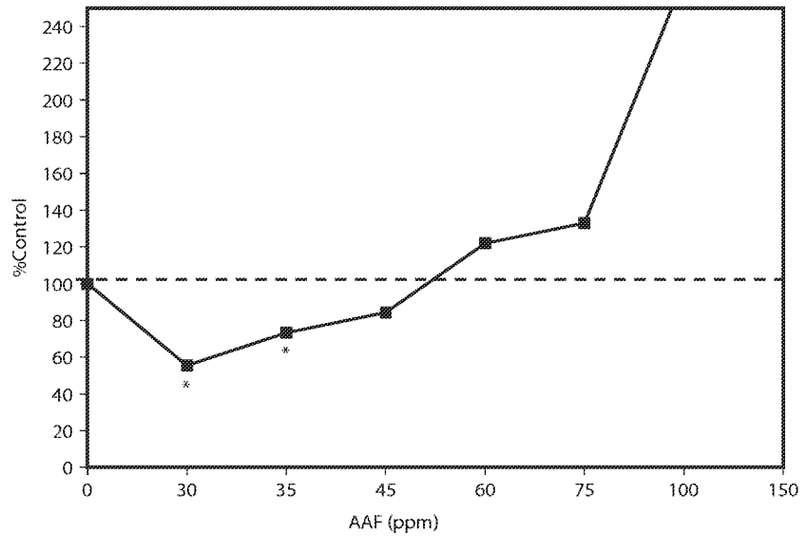
The selection of the threshold model by the regulatory community therefore was never validated throughout the twentieth century in the United States and internationally as well. It was adopted for use by regulatory agencies such as EPA, OSHA, FDA, and all state regulatory agencies. It guided the testing of all chemicals and drugs for safety. The hazard assessment process also assures the testing of agents only at very high doses and with animal models that were given no consideration whether an alternative dose–response model might exist, such as the HDR model. In fact, it would have been a useful factor for this type of interpretational flexibility to have existed.

### Attempt to Validate the LNT Model: The Megamouse Study

In contrast to the failure of governments to attempt to validate the threshold dose–response model, the US FDA made an effort to validate the LNT dose–response model for chemical carcinogens. The strategy involved the selection of a well-studied chemical carcinogen (i.e., 2-acetylaminofluorene [2-AAF]) and evaluation of it in a massive experiment that used about 24,000 mice. The results of this massive study were extensively reported [194–196] and assessed in detail by a special expert panel of the US Society of Toxicology [197], highlighting the importance of the study. While the findings generated much discussion and debate, a major point of agreement was that the study was only able to assess tumor incidence to the level of 0.01. The report was therefore called the ED01 study. This was the most striking finding since it required about 24,000 mice and all that could be judged were risks to $10^{-2}$ when regulatory agencies need estimates to the $10^{-5}$ or $10^{-6}$ for de minimus risk estimates. It was not possible, therefore, to practically validate the LNT model for cancer risk assessment at the levels of risk that regulatory agencies need to estimate. As a result, no other rodent-based megamouse study estimate has been subsequently undertaken to validate risk in the low-dose range.

Despite these concerns and limitations, the SOT committee developed a dose-related time to tumor model evaluation. They found that the 2-AAF induced a J-shaped dose–response for bladder cancer, a finding that was consistent in all six rooms in which the large numbers of mice were maintained (Figure 3.24). The SOT expert committee unequivocally stated that there was both a threshold reduction and a significant reduction in risks at doses below the threshold. Without using the term, the SOT panel concluded that the experimental findings demonstrated an HDR. This striking AQ17


ED_002751_00030366-00030




AQ18 **FIGURE 3.24** Bladder tumor incidence adjusted for time in ED01 megamouse study: HDR relationship. (Based on Bruce, R.D. et al., *Fundam. Appl. Toxicol.*, 1, 67, 1981.)

conclusion of the SOT panel was buried in the details of an analysis and was never widely cited. Yet, this is a principal finding of the largest rodent experiment, with a strong prospective study design to determine the nature of the dose–response in the low-dose zone. However, these results did not fit the preestablished regulatory agency LNT paradigm and were ignored by such agencies and the field of toxicology.

The validation of the LNT could have been undertaken by a far less expensive strategy and with the testing of more agents so that the issue of generalizability could be considered. For example, Japanese researchers assessed the dose–response for the liver carcinogen DDT using liver
AQ19 foci as the endpoint (Figure 3.25). The study was far less expensive and provided data using considerably less time; once again, the LNT model was not as supported as the hormetic model was.

### Hormesis: Dose–Time Response (Overcompensation) Studies AQ20

Biphasic dose–responses are typically graphed as either an inverted U-shaped dose–response or J-shaped. The graphing of the inverted U- or the J-shaped seems to be a discipline-specific feature with those reporting disease incidence using J-shaped graphing and those disciplines reporting on growth or changes in longevity using the inverted U-shaped dose–response.

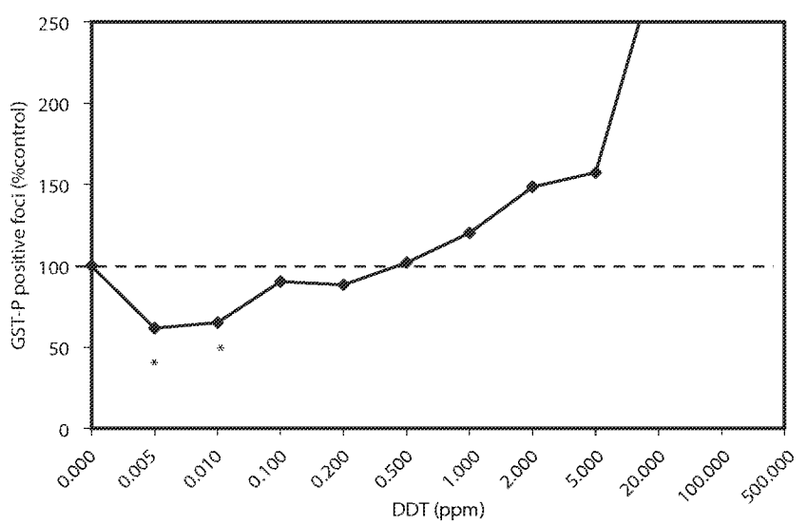



**FIGURE 3.25** Effect of DDT on liver foci formation in male F344 rats: HDR relationship. (Based on Sukata, T. et al., *Int. J. Cancer*, 99, 112, 2002.)



ED_002751_00030366-00031

The biphasic dose–response can also be not only dose-dependent but time-dependent as well. The biphasic dose–response can occur as a result of a direct stimulatory response at low dose followed by a high-dose inhibitory response (Figure 3.23). In contrast, the biphasic dose–response may also occur as a result of an initial dose-dependent decrease in response followed by an overcompensation response that over time yields the biphasic dose–response relationship [198,199]. At the lower doses, the compensatory response results in the response modestly exceeding that of the control group. However, at the higher doses, the compensatory response tends to fall short of a return to the control value. The resulting dose–response appears biphasic. Of particular interest is that the quantitative features for those dose–responses that are directly stimulatory and those that are compensatory are similar quantitatively, in fact, being distinguishable.

The compensatory stimulatory response has been widely observed in the pharmacological domain, with this type of response becoming very frequently cited since the early 1990s. The term *rebound effect* is widely used by researchers whose study designs typically include a dose and a time component. Dose–responses with the so-called rebound effect typically exhibit the same quantitative features of the HDR. In fact, in most cases, those dose–responses are examples of hormesis. For example, in the field of herbivory [200], it is commonly observed that following a low to modest removal of leaves, there is the occurrence of rebound effect in which there is an overcompensation of leaf growth. When excessive removal of leaves occurs, then the compensatory response is usually not adequate to return to control values. The quantitative features of the dose–response are strikingly similar to the hormetic–biphasic dose–response found in the toxicological literature. The term rebound effect is also commonly used in a wide range of biomedical disciplines as well. The use of multiple terms for similar phenomenon can make it difficult to gain a sense of the depth and breadth to which the HDR concept may have been studied.

### Hormesis: Plasticity

Why would very large numbers of dose–responses using different biological models with different endpoints and inducing agents with or without a time component show biphasic doses with similar quantitative features, that is, similar magnitude and width of response? Such a highly diverse group of dose–response parameters showing similar quantitative dose–response patterns is not consistent with a random process. Given its general nature, it may have been highly conserved during the evolutionary process of natural selection. The consistency of this response across the plant and animal kingdoms is striking and indicative of an inherent adaptation consistent with providing an estimate of biological plasticity across biological systems, independent of endpoint and inducing agent and differential levels of biological organization.

The integration of the concept of biological plasticity into the interpretation of the dose–response is a novel one [201]. Plasticity has often been considered within several descriptive contexts. The adaptability of the brain with respect to repair following injury has been described as a manifestation of biological plasticity [202]. In a comparable manner, the variation in plant structure and form along a long and progressively steep mountain side would be another example of biological plasticity [203]. In the case of the plant example, plants experience numerous changes in the physical environment along the progressive mountain slopes. There would be changes in carbon dioxide and oxygen concentrations, temperature, soil types, access to nutrients, soil microbes, and many others. These changes along the slopes of the mountain affect the induction of the altered plant phenotypes displaying a range of plasticity changes within such a setting.

The examples of the plant alterations up a mountain side are changes that reflect the impact of numerous biological adaptations in response to alterations in environmental parameters (e.g., oxygen/$CO_2$), some of which conform to a dose–response gradient. While the changes in plant phenotype reflect biological plasticity, this example is one of the complexities with multiple variables. However, the field of toxicology can explore similar types of gradient changes with alterations in chemical or radiation dosage while keeping all other variables constant. In this manner, the change in treatment will affect the formation of new phenotypes that reflect biological plasticity [201]. The low-dose stimulation seen in the HDR is a manifestation of biological plasticity, a change in biological phenotype. It reveals how much gain or capacity there is for change. The HDR reveals that biological plasticity in response to a vast array of endogenous agents as well as exogenous chemicals is consistently very modest, being in the percentage range, that is, at maximum only about 30%–60% greater than background or control exposures (Figure 3.23). This observed biological plasticity capacity represents how the field of toxicology can interpret this concept within a dose–response context.

The limits of plasticity provide a biologically based resource management system. Large numbers of biological endpoints display HDRs. All have plasticity constrains in the low-dose region. Such responses are operational as part of normal living activities and under stressful conditions. In order to maintain stability in the management of limited biological resources, one strategy would be to regulate the allocation of such resources and to manage how they are handled. The low-dose stimulatory response displays how the *system* controls resources at multiple levels of biological organization and it does so by the use of the hormetic stimulation. The significance of this type of resource management strategy is seen across all types of life, from microorganisms to humans, representing a biological adaptation that is highly conserved. Thus, hormetic stimulation within the context of the dose–response plays a fundamental role in evolutionary biology. The HDR has the capacity to affect how evolutionary biologists consider dose–response processes.

The low-dose stimulation measures biological performance within the bounds of an overarching system of biological plasticity. The stimulation reflects an enhancement of integrated response endpoints, such as cell proliferation, wound healing, or memory. In each case of such integrated


ED_002751_00030366-00032

endpoints, there is a limitation for its enhancement that is determined by the constraints of plasticity that is described by the quantitative features of the HDR.

At the time that the HDR was beginning its resurgence, another term was emerging in pharmacology called the *ceiling effect*. This term has generally been used to signify *the quantitative maxima* of a low-dose stimulatory response. The ceiling effect in pharmacology has been therefore used as another manifestation of the concept of biological performance within the framework of an HDR.

In 1907, Alexis Carrel stated that he hoped to find agents that would accelerate wound and other types of healing by 10–50-fold [204]. He hoped that broken bones could be healed in a few days rather than months. Yet, after more than a century, most reported attempts to accelerate healing show enhancements that are in the hormetic stimulatory range [205]. ~~Yet, there~~ is little doubt that rapid bone fracture healing (and other types of wound healing) would have important survival advantages. Thus, the degree of enhancement of repair is limited by the constraints of plasticity having a response *ceiling* in the percentage rather than fold zone, that is, being a manifestation of hormesis.

The concept of plasticity is also applied to biological regulation within the context of dose–response as these affect essentially all physiological systems and their control functions. Such low-dose regulatory-based responses represent a measure of biological performance, and such performance-related endpoints are in striking contrast to responses typically measured at the upper end of the dose–response spectrum.

The dose–response should not be interpreted as a simple continuum of agent-induced responses that increase or decrease in a monotonic manner. Substantial findings reveal a markedly different general dose–response pattern. That is, the effects that occur above the toxicological and pharmacological thresholds are often fundamentally different than those that occur below the threshold. The responses at high doses in the field of toxicology are typically, but not always, related to the induction of cellular and tissue damage, that is, true toxic responses. However, below the threshold, the response is not only adaptive but the means by which enhancements of responses occur and controlled and how these upregulated responses improve the chances of prolonged survival.

The dose–response therefore within a hormetic context is one of the low- and high-dose effects with very different biological response meanings. At the high end of exposure, one often encounters system toxicity; the high-end exposure can also reflect a system regulatory function in which the response may be slowed down via a receptor desensitization phenomenon or signaling pathway slow down, inactivation, or other alternative mechanisms. For example, low doses of anxiolytic drugs decrease anxiety in rodent models, while at higher doses, there is often an increase in anxiety. In rodent models, which prefer dark areas, low doses of anxiolytic drugs enhance the time spent in both open and lighted areas. This has been interpreted as a sign that the rodent overcomes some of its inherent anxiety of lighted zones. This suggests that there is an increase in traits such as curiosity and exploration. However, at higher doses, these behavioral patterns are reversed. From an evolutionary perspective, it would be an advantage to have the capacity to be curious and exploratory as well as cautious depending on the situation. Thus, the biphasic dose–response can be seen as displaying behavior patterns that are based in systems biology and of a regulatory nature.

### Summary of Hormesis Challenges to the Threshold (and Linear) Dose–Responses

The HDR should assume a central role in the field of toxicology. Table 3.3 lists hormetic principles, while Table 3.4 summarizes scientific developments concerning HDRs. The amount of data indicating this biphasic dose–response is extensive and reproducible. There is also a substantial amount of mechanism understanding of HDRs that are based on receptor-mediated processes linked to signaling pathways. A key feature of the HDR model is that it is highly generalizable, being independent of biological model, endpoint, and inducing agents. The HDR model has illustrated biological and toxicological complexities that were either ignored or underappreciated for decades by the toxicological and pharmacological communities. For example, the low-dose

**TABLE 3.3**
**Hormetic Principles**

Low/modest stress induces prosurvival responses.

The quantitative features of the HDR are similar across species and individuals and independent of differential susceptibility and agent potency.

The magnitude of the stimulatory response is constrained by and defines the plasticity of the biological system.

Hormetic responses occur at multiple levels of biological organization, the cellular, organ, individual, and population.

Downstream processes integrate responses from multiple independent stressor agents/excitatory stimuli to yield an integrated dose–response (i.e., molecular vector) reflecting the HDR.

Hormetic responses reflect both a general response to environmentally induced stress/damage and some elements of chemical structure specificity for endpoint induction.

*Source:* Calabrese, E.J., *Am. J. Pharmacol. Toxicol.*, 3(1), 56, 2008.



ED_002751_00030366-00033

**TABLE 3.4**
**Major HDR Observations**

Most commonly observed dose–response relationship.
Distinctive quantitative features, making it a unique biphasic dose–response relationship.
Most unique feature is the modest magnitude of the stimulatory response, usually less than twice control values.
The low-dose stimulation can occur via a direct stimulation or via an overcompensation to a disruption of homeostasis.
HDRs may be seen as an adaptive response that ensures tissue repair in an efficient manner and protects against damage from subsequent and more massive exposures.
HDRs are highly generalizable, being independent of biological model, endpoint measured, and chemical class.
Numerous specific mechanisms have been reported to account for HDRs.

*Source:* Calabrese, E.J., *Am. J. Pharmacol. Toxicol.*, 3(1), 56, 2008.

**TABLE 3.5**
**Implication of Hormesis for Toxicology/Risk Assessment and Clinical Practices/ Pharmaceutical Companies**

**Toxicology/Risk Assessment**

Changes strategy for hazard assessment, altering animal model and endpoint selection, study design including number of doses, and dose range and number of subjects per dose
Alters biostatistical modeling to predict estimates of response below control background disease incidence
Differentiates dose optima (i.e., benefits) for normal and high-risk segments of the population
Creates evaluative framework to assess benefits or harm below traditional toxicological threshold
Creates new framework for quantitatively altering the magnitude of uncertainty factors in the risk assessment process

**Clinical Practices/Pharmaceutical Companies**

Drug performance expectation will be constrained by the quantitative features of the HDR.
Drugs that are designed to act at high doses may have hormetic effects at low doses with possible undesirable effects (e.g., tumor cell proliferation).
Modification of biological set points will be constrained by the quantitative features of the HDR.
Clinical trials need to recognize interindividual variation in the HDR.
Clinical trials need to be designed to take into account the quantitative features of the HDR.

*Source:* Calabrese, E.J., *Am. J. Pharmacol. Toxicol.*, 3(1), 56, 2008.

stimulatory effect can be beneficial or harmful effect. The effects may also be time-dependent. These factors indicate that the hazard assessment as used by regulatory agencies would have to be modified in order to take into account of the possibility of HDRs (Table 3.5); such changes would include alterations in the hazard assessment protocol, in study design (i.e., number of doses, dose spacing), sample size, and statistical power strategies and the need for replication. It may also affect the choice of the biological model with special consideration given to control background values and the variability of key endpoints. Table 3.6 briefly summarizes historical factors that impeded or prevented the concept of hormesis from being accepted by the toxicological community and by regulatory agencies within the risk assessment process.

## Challenge #3: Pharmacology and the Biphasic Dose–Response

The historical foundations of the dose–response relationship in pharmacology were largely based on the classic research of Alfred J. Clark [35,36,68] and his contemporary and successor John Henry Gaddum [80,206]. Based on extensive research on the quantitative actions of drugs such as acetylcholine and atropine, these authors showed that combining of drugs with specific receptor groups could be mathematically similar to the function used in the Langmuir (1918) adsorption isotherm. The responses of a tissue were assumed to be directly proportional to its specific receptor groups as occupied by the drug, the receptor occupation followed the law of mass action, and drug molecules would have equal access to all receptor groups. This perspective became the dominant pharmacological dose–response paradigm for the remainder of the twentieth century. AQ21

Despite its general intellectual dominance within the field of pharmacology, this dose–response model of Clark and Gaddum needed further development, refinement, and correction over the subsequent years. In fact, not long after the theoretical formulation by Clark [35,36], it was found that adsorption equations besides that of Langmuir's could fit the dose–response data just as well and that a maximal response


ED_002751_00030366-00034

**TABLE 3.6**
**Factors Contributing to the Historical Demise of Hormesis**

- Powerful conflicts with traditional medicine and homeopathy.
- Toxicology directly emerges from traditional medicine.
- Influential opponents to the hormesis concept controlling the vehicles of communication.
- Influential opponents (radiation) accepting data that supports hormesis and denying that it is hormesis.
- Biostatistical modeling being constrained to deny hormesis.
- Rejection of hormesis occurring during the period of toxicological concept consolidation.
- No intellectual counterforce at the time of concept consolidation (not yet addressed).
- Early supporters of the hormesis concept lack understanding of its dose–time response features.
- Hormesis being difficult to prove experimentally without proper study designs.
- Powerful regulatory agencies adopting rival dose–response models.
- Governmental hazard assessment protocols making it highly unlikely to observe hormetic effects.
- Being shunned from standard texts, society meetings, and academic teaching.
- Being excluded from research funding possibilities in major governmental grant programs.
- Biological/societal implications not appreciated nor anticipated.

*Source:* Calabrese, E.J. et al., *Toxicol. Appl. Pharmacol.*, 222, 122, 2007.

may not require maximal receptor occupation. However, despite such limitations in this pharmacological model of the dose–response, it became adopted along with the belief that the maximal response required the complete occupation of receptors by the agent [207].

While the previous conceptual framework of the pharmacological dose–response has had a long history of qualitative predictive utility, it frequently offered less than satisfactory quantitative agreement with experimentally AQ22 derived data [208]. It was often reported that the observed dose–response did not follow the predicted form (some drugs [i.e., partial agonists] often stimulated tissues but did not produce the expected normal maximum response), nor could the model of Clark and Gaddum account for the antagonism shown by partial agonists to more powerful agonists, tissue desensitization following exposure to highly specific stimulants (acetylcholine, histamine), as well as responses when a vigorous excitation is quickly replaced by competitive antagonism [165].

These and other limitations lead to modifications in the receptor-based dose–response concept during the mid-decades of the twentieth century. Ariens [209] proposed that the drug–receptor union may have varying effectiveness, which he called *intrinsic activity*, while Stephenson [208] referred to this concept as *efficacy*. This efficacy or intrinsic activity concept was expressed quantitatively as the rate constant of the second step of a drug–receptor process that yields the active form of the drug. This concept was based on the studies on motor-endplate depolarizing activity [210–212].

Biphasic dose–response curves, especially those with a single active chemical group, offered a further significant challenge to the occupation receptor theory, proposing that such curves may be observed if a drug interacted with two-receptor systems [213]. In this context, Dale in 1906 [166] noted that adrenaline can act at both excitatory and inhibitory receptors in the vasculature; this observation lead Furchgott [214] to suggest that these receptors may occur on the same smooth muscle cell. By the 1960s, numerous, yet isolated, biphasic dose–responses were reported for drugs of pharmacological importance. These responses were accounted for by the presence of two opposing receptor populations. In his subsequent assessment of this literature, Szabadi [165] reported that most of the sympathomimetic amines activate opposite receptors in smooth muscle preparations with α-type receptors being stimulating, while β-receptors were negative. Likewise, by the 1970s, several researchers reported that histamine can activate both excitatory and inhibitory receptors [215,216] with $H_1$-type excitatory receptors being stimulating and $H_2$ receptors being inhibitory.

It also became recognized that two opposing receptor populations to the same agonist were often present on the same neuron consistent with the early suggestion of Furchgott [214]. This was the case of invertebrates for acetylcholine [217], dopamine [218], 5-HT [219,220], and histamine [221] on sympathetic ganglion cells along with numerous other examples.

As a result of these cumulative findings, Szabadi [164,165] proposed a theoretical model to explain how agonists and antagonists act in pharmacological systems containing opposite acting receptors. This model was derived from the combination of *double agonists* and functional antagonism as proposed by Ariens et al. [222]. Double agonism was generally defined as a phenomenon when a compound induces an effect by interaction with two different specific receptors. The Szabadi [165] model was a special case of double agonism when two receptors, which are activated by the agonist, mediate opposite effects. If the two types of receptors are assumed to be functionally independent, the model for functional antagonism is employed; the quantitative features of the model are described by the algebraic sum of the induced effects produced by the activities of both receptors.

The model of Szabadi [165] is very generalized, with the potential to account for a wide range of dose–response


ED_002751_00030366-00035

relationships depending on assumed affinities and intrinsic activities. This model may also account for hormetic-like biphasic dose–response relationships. Since the publication of the Szabadi [165] model, the number of examples of biphasic dose–responses has markedly increased, including nearly 40 receptor families affecting a range of biological endpoints that govern essential physiological and behavioral functions [186–188].

The biphasic dose–response model of Szabadi [165] has been supported and extended by other researchers [168,169,223–225]. For example, based on research on α-lactalbumin production by rat mammary gland explants, Quirk et al. [226,227] were able to account for biphasic dose–responses even for highly specific glucocorticoids with binding to a single receptor. This response was accounted for with a model of a single *turn-on* nuclear receptor site for glucocorticoid receptors and multiple glucocorticoid regulatory refinements. This finding was consistent with those of Jarv that agonistic and antagonistic effects of ligands may be related to their binding in two separate sites of the same receptor molecule [228,229]. Evidence supporting this model was reported by Jarv et al. [230] for the muscarinic acetylcholine receptor.

While pharmacological evaluation of biphasic dose–responses has dominated the literature from the 1970s to present, there is both a convergence of concept and a reformulation of such perspectives in the area of toxicology and more broadly in systems biology. In 2004, Leuchenko et al. [231] presented a framework for biphasic regulation that is conceptually similar to the model of Szabadi [165] and the considerable research on the concept of hormesis. Leuchenko et al. [231] proposed four types of biphasic regulatory schemes, with the first two being similar to the one-receptor model [223,232] and the one-agonist two-receptor model [165]. However, the paper added a further dimension of progressive complexity.

In the third model (i.e., type III), the biphasic response results from signal transduction activities that are removed from the response element (ligand–receptor complex). In this situation, the biphasic nature of the dose–response derives from the properties of the signal-transducing components. The authors proposed a variety of ways in which the biphasic dose–response could occur depending on the type of properties of the RE, molecular inputs, and complexity of the biochemical pathways. An example of the type III biphasic regulation is seen with mesoderm induction in *Xenopus laevis* via the TGFB homologue that activates the genes *Xbra* and
AQ23 *goosecoid*. The activated receptor starts the signaling process by phosphorylating a signal transduction of the SMAD family that leads to gene transcription. Approximately 100 and 300 activin molecules need to bind the receptor to activate Xbra and goosecoid expressions, respectively. However, the expression of Xbra is suppressed by high goosecoid concentrations. Consequently, when activin activates about 100 receptors, Xbra expression is positively regulated, but if the activin concentration is increased by about 30-fold, goosecoid expression is enhanced, resulting in turning off Xbra expression.

The fourth model of biphasic regulation requires two inputs to affect the response rather than one as in the previous cases. This is seen in combinatorial inhibition when a molecule binds with two or more interacting molecules to form a single functional complex as is the case with scaffold proteins. A second type IV receptor involves two or more interactions between an activator and the activated molecules for full activation. Examples of both biphasic regulation with scaffold protein concentrations and distributive activator are seen in the MAPK cascades. Leuchenko et al. [231] speculated on the adaptive significance of biphasic regulatory strategies. They provide tunable filtering of the magnitude of the incoming signal and determine the sensitivity and strength of the response. The composite of these strategies may be seen as a framework of broad biological significance at multiple levels including global and local domains.

## Challenge #4: Population-Heterogeneity-Based LNT AQ24

While it is often stated that each individual of the population may display a threshold response, the population itself may display no threshold due to normal heterogeneity within the highly outbred and socially and culturally diverse human population. While this is a conceptually logical statement, it is principally a theoretical one. The reason for this statement being theoretical is because the power of epidemiological studies to estimate low risks in the population is usually weak, due to limitations in assessing exposure, genetic variability, and numerous other disease and performance-modifying variables.

The principal controversy associated with the population-heterogeneity-based LNT hypothesis is the generalization of AQ25
its applications to agents and endpoints, including those of a noncancer nature. It is also not clear how this concept would translate into what is permissible population-based risk [1]. However, as noted earlier, the 1977 SDWC [148] used this concept as one of their eight guiding principles to support the LNT model for carcinogens. Thus, this concept is not a new one—but one now reformulated to challenge the threshold dose–response for noncarcinogens. Would each adverse effect be treated in a similar manner, that is, with the same level of permissible risk, or would the permissible risk be related to the medical implications and cost of therapeutic interventions? This concept would appear to offer a profound challenge to regulatory agencies and would affect a reevaluation of environmental, food, and occupational chemical health standards.

The scientific foundations of a heterogeneity-based LNT model assume that there are multiple risk factors affecting susceptibility to all toxic substances and that these risk factors are randomly distributed within the population. This would be predicted to result in a rather broad distribution of susceptibilities with multiple interactive risk factors affecting a progressively smaller proportion of the population who would display a progressively greater level of risk and/or susceptibility. When taken to its extreme, those individuals with the greater number of significant risk factors will be the first to experience adverse effect and premature death.


ED_002751_00030366-00036

The heterogeneity-based LNT concept also assumes that there is an additive to background adverse effect relationship providing further support for a linearity interpretation.

The underlying evidence to support the heterogeneity-based LNT is difficult to obtain since epidemiological methods have generally been shown to be hard to establish causality unless the risks exceed the control or reference population by a factor from two- to threefold. In the area of toxic torts, formal judicial guidance reflects this perspective, with judges being guided not to accept a causal relationship unless the related risk for the alleged exposure equals or exceeds a factor of 2 [233]. If, therefore, the population heterogeneity-based LNT dose–response model were to be accepted, it would come into conflict with the current standard for epidemiological guidance for tort-risk causality [234].

Despite the long-standing two- to threefold epidemiological causality rule of thumb as just discussed, this perspective has been challenged, especially with the area of fine particulates and community-based air pollution [235]. Numerous large-scale epidemiological studies in the United States and elsewhere have generally reported relative risks that have ranged from the slightly below 1 to about 1.2. Some investigators and regulatory agencies, especially in the state of California, have concluded that causality in such studies can be affirmatively made, even with population-based risk, below twofold increased risk historical perspective. This has been a highly contentious matter since it is difficult to accurately identify known causes of deaths as well as underlying biological predispositions. Factors such as family characteristics, age, gender, stress, diet, prior disease, access to medical treatments, social factors, epigenetics, and other influences are likely factors affecting health outcomes. Given all the possible confounding variables and the extreme difficulty of their quantification or the general inability to control for such differences with surrogate parameters such as socioeconomic and other standard parameters, the capacity to use epidemiological methods to estimate risks to the less than the doubling rate is generally beyond the present capacity of this discipline. Thus, the population-based heterogeneity-based LNT model is limited by the inherent limitations of epidemiological methods. Even with marginal improvements in the sensitivity of epidemiological methods in the future, its capacity to address low-dose risks is principally theoretical and model dependent and has no capacity for validation. While this is a powerful argument against the acceptance and use of the population heterogeneity-based LNT, it would be similar to an argument against a toxicologically based LNT model based on experiments in which only a few very high doses were used within the standard chronic bioassay.

## ISSUES

### Dose–Response versus Dose–Time Response Relationships

The effects of the dose on biological systems may be expected to change over time. Biological systems are dynamic; they can be stimulated, stressed, or injured, and in response, such changes may display a wide range of adaptive or maladaptive processes. These responses to toxic substances may also affect the availability and utilization of various biological resources and the capacity of the system to respond to subsequent similar or different exposures. There is therefore value if experiments can assess such biological responses over time. In practical terms, investigators are typically confronted with a decision over whether to use a range of doses or to follow the response of a single dose over a range of time points. Combining these dose and time features would be the ideal research strategy as much is lost by the ignoring the other.

The fact that biological systems are dynamic and adaptive has long been known, first being explored in the 1890s [44]. Of particular importance to the history of dose–response was the work of Sarah Branham in 1929 [38], which was designed to provide a detailed and updated replication of the seminal findings of Hugo Schulz [23,24] on the effects of numerous chemical disinfectants on the metabolism of yeasts. Of particular interest was that Branham [38] assessed the effects of multiple chemicals over multiple concentrations each over multiple time periods. What Branham [38] demonstrated was that these agents initially induced a concentration decrease in metabolism. However, this was subsequently followed by a compensatory or rebound-type response that eventually led to a stimulation within the lower concentration range. Compensatory responses were also noted at the higher concentrations, but the degree of compensation was usually not enough to overcome the toxicity that was initially induced. The degree of stimulation was modest, being at maximum in the 30%–60% zone greater than the control values. Similar dose–time responses have been widely reported confirming the general nature of the dose–time overcompensation responses [199]. Such findings indicate the significance of study designs that include a broad range of doses along with multiple measures over time. Failure to incorporate both adequate dose and time point evaluations will lead to inadequate understandings of the dose–response. Unfortunately, the use of many doses and their evaluations over multiple time controls is resource intense. However, the value of such consideration is clearly represented in the work of Branham and others [199]. These findings reveal the dynamic nature of the biological affected systems when it is stressed and/or injured. The dose–response, therefore, is not static and the dynamics of cellular/system response are necessary to discern as it provides critical information of not only dose-induced damage but critical repair and recovery processes. In fact, it was the use of the time variable that provided the capacity to discover the phenomenon of preconditioning and postconditioning in the biomedical sciences and the adaptive response to radiation and chemical mutagens as seen in the following. AQ26

### Adaptive Response/Pre(Post)-Conditioning/Auto Protection

Another factor affecting the dose–response is the physiological state of the biological system. Prior exposure to an



ED_002751_00030366-00037

agent can affect how the biological system will respond to subsequent and more massive exposures of the same or different agents. This phenomenon has long been recognized by different terms in the toxicological and biomedical sciences. A low dose of $CCl_4$, which caused a negligible toxic response to the liver based on the change in serum levels of AST and ALT, prevents rats from dying when they receive a subsequent $LD_{95}$ dose of the same agent [236]. This phenomenon was called autoprotection, that is, a prior low dose of the chemical prevented adverse health effects caused by a subsequent and more massive exposure of the same agent. It was later shown that a prior dose of a similar but not identical agent could protect against a massive exposure of the similar toxic agent (i.e., heteroprotection). The mechanism of protection was widely thought to result from the possibility that the low prior dose may have reduced the cytochrome P450 activity, preventing the bioactivation of the $CCl_4$, thereby reducing the toxic potential of the subsequent massive exposure. This interpretation was challenged by Mehendale [237,238] who associated the enhanced survival due to the prior low dose with an accelerated process of hepatic tissue repair.

The concept of an autoprotection and heteroprotection for heavy metals was also reported during the same general time period. Yoshikawa [239] found that a pretreatment with low doses of various heavy metals could markedly reduce the acute toxicity of similar and other heavy metals in a mouse model. These findings were further evaluated over a broad dose range of the preconditioning/priming agent. A biphasic dose–response was reported for lead and mercury fully consistent with the quantitative features of the HDR.

That a low dose could protect against the effects of a subsequent more massive exposure was subsequently generalized to the field of chemical mutagenesis by Samson and Cairns [176] and for radiation-induced mutagens by ~~Olivier~~ et al. [177]. These investigators referred to the phenomenon as adaptive response. Two years later, it was shown that a prior hypoxic stress to the heart of dogs reduced the toxic effects of a subsequent massive myocardial infarction, a phenomenon referred to as preconditioning [178]. Thus, the fields of chemical toxicology, chemical/radiation mutagenesis, and biomedical/pharmacology converged on the same low-dose–high-dose protection phenomenon and referred to this with differing names. These observations in each case were replicated and generalized, covering significant areas of research. Furthermore, in the aftermath of the research on preconditioning, investigators reported the phenomenon of postconditioning. That is, if the low dose was given after the more massive exposure, it affected a similar decrease in toxicity as the preconditioning phenomenon dose [240].

The autoprotection, adaptive response, and pre-/postconditioning phenomenon act via the use of an adaptive dose that induces mechanisms that reduce the toxicity of a larger dose. Of particular significance is that the magnitude of the protective response depends not only on the timing of the adapting dose but also on its dose level as well. That is, all adapting doses are not equal in their capacity to affect a protective response. Subsequent research revealed that the adaptive dose could be optimized. Detailed dose–response studies using a broad range of adapting doses were found to follow the hormetic–biphasic dose–response. This was also the case for postconditioning responses as well [240].

## High-Risk Groups: Dose–Responses

The dose–response may be affected by a wide range of biological factors, including developmental processes, age, gender, dietary and nutritional status, genetic factors, preexisting disease conditions, and prior exposure history, among other factors. These conditions can be seen as either enhancing or reducing one's susceptibility to toxic substances, thereby altering the shape/slope of the dose–response. Since all individuals experience developmental and aging processes, there will be periods during the normal life cycle in which all people will be at enhanced risk to certain agents. In general, it is thought the young will be at enhanced risk to most, if not all, toxic substances. While this concept has been generally borne out in a wide range of toxicological studies, there are instances where the young are not more susceptible than a middle-aged population subjects. In fact, there are well-known situations (e.g., renal toxicity for fluoride and mercury) for which their risks are significantly lower [241]. These observations illustrate challenges that regulatory agencies confront in the assessment of risk.

The enhanced susceptibility within the high heterogeneous population is thought to be captured with a range of 10-fold starting from the median response of the normal population response [65]. This is a practical guidance value that has not been systematically assessed. For example, the effect of oxidative stressors on normal red blood cells can be assessed in a dose–response context. These cells could be compared with the response of red blood cells from individuals with various types of antioxidant enzymatic deficiencies (e.g., glucose-6-phosphate dehydrogenase [G-6-PD]), proceeding from moderate to more extreme [242]. Such experiments could provide information on differences in the magnitude of the cell damage at the same concentration as well as the differential threshold concentrations for each experimental subgroup. These population-based subgroups could be made even more complex by superimposing factors such as lower or higher exposure to dietary antioxidants, further affecting the threshold and magnitude of response.

## How Physiological Status Affects the Dose–Response: The Anti-Inflammatory Phenotype

Low-level exposures to ionizing radiation can enhance several immune parameters while being inhibitory at higher concentrations [243]. These findings are in striking contrast to a rather large body of experimental data that demonstrates that low doses of ionizing radiation can have a depressive effect on immune functions if the biological system is in an inflamed condition [47,244–246]. In fact, the dose–response in this situation is U- or J-shaped. That is, at the lower doses, the ionizing radiation suppresses the inflammatory


ED_002751_00030366-00038

condition, while at higher doses, it inflames it further. This phenomenon has been documented in five arthritic animal models with strong consistency [47,247–256]. Much follow-up work has been conducted on the underlying mechanisms contributing to the radiation-induced suppression of inflammation [257–265]. The key conceptual insight offered is that the dose–response relationship is dependent on the physiological state of the organism. At the same doses, the response could be opposite depending on whether the biological system was inflamed or not. Low doses of ionizing radiation can therefore induced two types of HDRs: one that enhances immune function at low doses and one that suppresses the immune-mediated inflammatory state, thereby creating an anti-inflammatory phenotype.

### Triphasic Dose–Responses

While the principal focus on the assessment of dose–response relationships has been directed toward threshold, linear, and hormetic/biphasic dose–responses, triphasic toxic responses have also been reported. However, the frequency of such reports is quite limited. Nonetheless, the occurrence of triphasic dose–responses is possible based on biological theory. There are significant challenges in the study of such possibilities starting with requiring more dose/concentrations. A particularly interesting example of a triphasic dose–response relationship was presented by Hooker et al. [266] in an assessment on x-ray-induced mutations in the spleen of pKZ1 mice. At the high end of the exposure spectrum, the x-rays, as expected, enhanced the incidence of mutations. However, as the doses were lowered, the incidence decreased below that of the control group, demonstrating support for an HDR. As the dose was further diminished, the mutation rate returned toward the control value again, consistent with a hormetic interpretation. However, further reduction in dosing revealed a surprising and novel finding. The mutation incidence flared up again, significantly beyond that of the control group. The dose–response was triphasic, with an increase in the frequency of mutations, followed by a marked reduction below the control and then the increase at higher doses.

Radiation-induced triphasic dose–responses were also reported by Choi et al. [267] in zebra fish embryos, either one or two embryonic cells, irradiated by microbeam protons over dose range from 20 to 2000 protons. This study not only confirmed the occurrence of the triphasic dose–response but showed biological responsiveness down to the level of 20 protons.

Much data exist that could explain both the low-dose protection and high-dose enhancement of mutation. However, what could account for the increase in mutation rate at the lowest doses? While this remains an area of research, it may be hypothesized that at the very lowest doses tested, the x-rays/protons induced a low level of damage. However, in order for repair processes to be induced and the damage to be repaired, the damage signal must be first detected, thereby initiating the repair process. The question that is posed is how sensitive is the detection system in this particular biological model and to what type of damage. Thus, it has been proposed that the damage at low doses may reflect a level and type of molecular alteration that goes undetected and thus unrepaired, at least within the time period of the study observations.

These types of investigations raise a broad range of novel scientific questions concerning damage, detection, repair, the generalizability of this phenomenon to other tissues and biological models, and the adequacy of routine hazard assessment protocols to detect such effects. The issue of triphasic dose–responses and their toxicological implications is an intriguing area of study but is generally ignored by the regulatory and research communities. If these findings, as assessed in the mouse and zebra fish models, could be broadly generalized, it would have significant biomedical and risk assessment implications.

### Maximum Tolerated Dose/Dose–Response

The information provided from the chronic bioassay based on the use of MTD-related doses has had a controversial history. The MTD is the highest dose that a treatment group can be exposed to over the 2-year period of the rodent chronic bioassay without experiencing toxicity and/or a loss of more than 10% body weight. However, it was not uncommon for some chemicals, especially at the highest dose, to cause cell damage in areas such as the liver. Lower doses were typically believed not to cause such cell damage or to do so with lesser frequency and intensity. As a result of the cell damage at the MTD dose, cell proliferation responses might be initiated in order to repair this damage, providing a tumor promotional response resulting in an enhanced tumor incidence at the highest/MTD dose. It was often the case that there was a significant tumor response at the MTD but not at the lower dose(s) [268]. Nonetheless, regulatory agencies would make a carcinogen designation for such agents. Based on cancer risk assessment methods, these data would be modeled via an LNT process. This area has been highly controversial as the cancer risk assessment is significantly affected by a toxicity/promotional effect at the MTD [268–270].

### Shallow/Steep Dose–Responses

Descriptive considerations of the dose–response have revealed that some dose–responses are very steep, with the toxic responses occurring over a very narrow dose range. An example of this type of dose–response is seen with cyanide and its induced mortality. In contrast, some dose–responses are very shallow with toxicity occurring over a very wide dose range. An example of this type of dose–response would be petroleum. In general, a very steep dose–response is due to the fact that the risk factor is highly specific and not subject to a high degree of interindividual variation. In the case of cyanide, the reason for the steep slope is that this agent is not subject to considerable metabolism and its target for toxicity, that is, the key cytochrome oxidase is essential for energy/ATP generation, varies little between individuals.


ED_002751_00030366-00039

Thus, the toxic effects of cyanide would be quick in most, if not all, animal models and humans. In the case of petroleum, it is a complex mixture, comprised of thousands of chemicals with differing metabolic patterns and with differing targets and mechanisms of toxicity. As a result, there are likely a wide range of risk factors broadly distributed within a highly heterogeneous population, resulting in a far shallower dose–response.

### Cumulative Dose–Response versus Dose Rate Response

In the mid-1940s, the question was raised as to whether exposure to the same cumulative dose to ionizing radiation would result in the same degree of toxicity independent of the dose rate. This was a question raised during the Manhattan Project by the radiation geneticist Curt Stern at the University of Rochester since it was considered as a test for the linearity dose–response hypothesis. Initial studies assessed the effect of a broad range of x-ray doses administered to fruit flies (i.e., over seconds to minutes). The response gave evidence of a linear dose–response relationship. However, when the same cumulative exposure was given at a rate of only 1/15,000 of the acute dose, a threshold was reported. This was a seminal observation as it challenged support for the linear dose–response interpretation [144,271]. This challenge to linearity was believed to be so significant that Hermann Muller and Curt Stern, two of the most influential radiation geneticists, tried to prevent the acceptance of the findings of the Caspari research [10,29,39]. As noted earlier, research at Oak Ridge by William Russell with mice would support the Caspari findings and the belief that the genetic toxicity response to exposure was cumulative.

### Carcinogens: Latency and Dose–Response

The principal way in which dose is used to evaluate carcinogenic responses is via tumor incidence. However, in 1943, Hermann Druckrey [272] published the first of a series of papers [272–275] establishing a relationship between dose and the time required to detect tumors, that is, the tumor latency period. This introduced a new concept with the potential to affect significantly how carcinogen risk might be estimated in a manner that was more responsive to human risk than the more limited dose–tumor incidence methodology. The key observation was an inverse relationship between dose and tumor latency. That is, the lower the dose, the longer the time required for tumor appearance. It was hypothesized that if the dose were reduced low enough, the latency period could theoretically be longer than the normal life span of the experimental species. In an analytical sense, the treated groups in such low-dose zones would have a tumor incidence indistinguishable from controls. An attractive aspect of this concept was that one could accept the linear dose–response model and yet still arrive at a *practical threshold* for carcinogens. The proposal of Druckrey represented a type of toxicologically based compromise between the LNT and threshold dose–response models.

The Druckrey dose–latency tumor incidence concept generated considerable interest worldwide. Several researchers were quick to validate the findings of Druckrey [276]. AQ27
In the former Soviet Union, the concept of dose–latency was accepted in risk assessment practices by the late 1970s following its experimental validation by Yanysheva and Antomonov [277] for carcinogen benzo(a)pyrene. The authors stated that any carcinogenic effect of the benzo(a) pyrene would be observed only considerably after the normal life span of the species had been exceeded.

This idea also resonated with some leading researchers in the United States, including Hardin Jones at the University of California at Berkeley, an expert in human aging, especially with respect to the effects of ionizing radiation. He and his colleague Alexander Grendon published several papers that integrated the findings of Druckrey and others as well as new understandings of the process of carcinogenesis, deriving a predictive biomathematical model. In practical terms, Jones and Grendon [278] reported that if the dose were decreased by a factor of 1000 in the linear zone, the latency period would increase by a factor of 10. The Druckrey concept was also applied to the field of occupational cancer by Philip Enterline [279] at the University of Pittsburgh based on a meta-analysis of 11 major epidemiological studies of asbestos exposure and respiratory cancer.

Even though the findings of Druckrey were striking, substantially replicated and extended to a range of compounds, using animal models and epidemiological meta-analyses, it was rejected by US regulatory agencies, with the concept failing to be integrated into and/or affecting hazard assessment and risk assessment processes. Why would this be the case? On the historical side, Occupational Safety and Health Administration (OSHA) conducted massive carcinogen policy hearings during AQ28
1978 [280]. The dose–latency concept of Druckrey and Jones was considered. However, Druckrey did not testify nor did any other researcher who had published supportive findings of the dose–latency argument. Jones was expected to offer testimony but unexpectedly died less than 2 months prior to the hearings. His relevant papers were entered into the record and commented upon, especially by those opposed to having this concept affect carcinogen risk assessment policy. Without his presence to explain and defend his position on this topic, there was little likelihood that dose–latency tumor position would even partially prevail as several notable opponents (e.g., David Hoel, Umberto Saffiotti, Richard Peto, and Marvin Schniderman) would counter his written statements without any real opposition. The most impressive of the criticisms was that by Hoel (based upon a paper by Guess and Hoel [281]). This paper argued that the findings of Druckrey of an inverse relationship between dose and latency not only were not unexpected but would be readily predicted via stochastic modeling assumptions. Thus, there was nothing new in this concept. As a result, the concept of dose–latency for carcinogens was dropped from the cancer risk assessment process and the hazard assessment testing scheme.

A counter argument not presented was that dose and time to tumor is an important concept and there was no reason to


ED_002751_00030366-00040

restrict the assessment to only tumor incidence in the animal bioassay. A similar argument was made earlier by Albert and Altshuler [282,283] who argued for a novel approach in the extrapolation of laboratory studies in the derivation of environmental health standards. This approach incorporated the concept of age at the time of the appearance of an adverse health effect as well as its incidence, a position similar to that of Jones. Albert and Altshuler [282,283] stated that the usual approach for assessing carcinogenic risks such as providing the dose to incidence relationship could be extremely misleading and give an inappropriate degree of importance in the risk assessment/risk management process. The typical dose–incidence methodology used by regulatory agencies today fails to consider the age at which new tumors occur or the likelihood that additional carcinogen exposures could affect people who would have developed tumors from different causes. Supporting this perspective was a National Academy of Sciences [284] report, commenting upon the work of Albert and Altshuler [282], that it may be possible to establish standards for carcinogens that would limit the possibility of environmentally induced tumors to only very advanced age, with less than a 10% increase in the chance of cancer at 95 years of age. While 95 years of age may not seem as old today in the second decade of the twenty-first century than it did some four decades ago, the basic concept of the National Academy of Sciences was in agreement with the perspectives offered by Jones and Grendon [278] as well. Again, this OSHA hearing failed to bring forward representation of the National Academy of Sciences. Likewise, Albert and Altshuler, both prominent toxicologists, did not render testimony on this issue.

In the intervening years, several lines of research have supported the Druckrey/Jones perspective, revealing that it takes a higher dose of carcinogen to enhance tumor promotion than initiation. At higher doses, it is possible to turn on promoting processes that can markedly decrease the latency period. The reverse would also be the case. That is, at lower doses and with less promotion, the tumor latency would be extended. While the initiation process may well be stochastic in nature, this was not likely the case for the induction of promotion, which has been typically seen as demonstrating a threshold dose–response. Thus, the concept of dose affecting latency has a solid foundation, does not have to be associated with a stochastic process, and can provide a means to derive a practical threshold for carcinogens as originally intended by Jones. This area is likely to warrant considerable toxicological research as it has the capacity to profoundly affect the risk assessment process for carcinogens.

## Epidemiology and the Dose–Response

There can be considerable variation in the dose–response that subjects display toward the same agent. If there is a wide range in susceptibility (i.e., interindividual variation) and if hormesis does occur within the various subgroups of the population, how may this affect the overall population-based dose–response? This will depend on the nature of each subgroup's dose–response relationship and each subgroup's proportion of the overall population. Consider the following subgroup-specific dose–response relationship and their impact on the overall dose–response relationship for the population. We are assuming that there are five population subgroups (G1–G5) and each ~~have~~ a defined dose–response relationship. Subgroups 1 and 5 show no evidence of an HDR, but subgroups G2, G3, and G4 display unique HDR patterns. For simplicity, assume that each subgroup comprises 20% of the population. The population average, as represented by the bolded line (Figure 3.26), displays a threshold-like response. If the population proportions for each subgroup were changed, then the composite (i.e., average) response

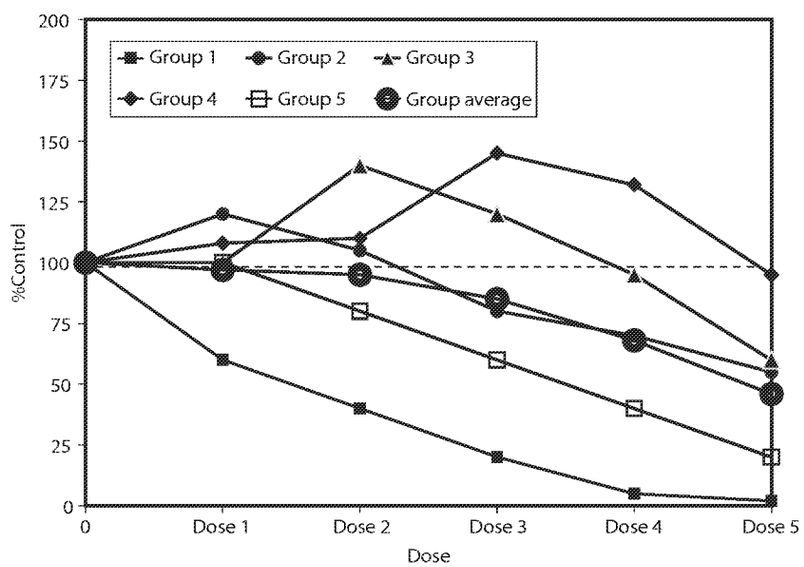



**FIGURE 3.26** Population subgroup and population average dose–response relationship.



ED_002751_00030366-00041

would also change. These findings demonstrate that a highly heterogeneous population has the potential to provide evidence that may or may not reveal a hormetic effect even when some of the subgroups display hormesis. This exercise demonstrates that the assessment of population-based data comparisons of substantial heterogeneity as may often be the case with humans may lead to findings that are not indicative of any underlying mechanism despite observed dose-dependent transitions. This is a situation that is not often appreciated, yet one with important biological and public health implications.

## DOSE–RESPONSE IN PERSPECTIVE

One cannot underestimate the influence of biostatistical dose–response modeling in risk assessment since the mid-1970s when the EPA made the policy decision to apply linearity at low dose for carcinogen risk assessment. EPA selected what it believed to be a model with reasonable biological plausibility (i.e., the multistage model). The problem with this policy is that *assumed* plausibility does not equal validation. There was some toxicological support for a linear interpretation starting with the first systematic dose–response studies that were published during WWII, in Germany [272], and later extended by Druckrey and Küpfmüller [273] using ~~bitter~~ yellow with five different daily doses ranging from 1 to 30 mg/rat. The administered total carcinogen doses were similar for all treated groups but that the median latency period (+) was inversely proportional to the daily dose. When plotted double logarithmically, the result was a linear dose–response relationship that followed a specific dose–time mathematical relationship in which the latency period for the time to the first appearance of a tumor was inversely related to dose. These findings were interpreted by Druckrey to mean that even very small daily doses of carcinogens could result in tumor development, that the doses were additive, and that the induction time is of considerable importance. Despite the fact that these findings clearly supported a linearity dose–rate relationship, they also indicated that latency was an important parameter that was affected by dose rate. Their data suggested that if the dose were decreased, low enough tumors would be predicted to occur long after the normal life span of the individual, in effect a practical population-based threshold. In a more statistical framework, the chemically induced tumor incidence would be indistinguishable from control group findings.

Another challenge to the linearity concept is that no LNT model, including the multistage model, could be validated in the low-dose zone. At the same time, numerous inconsistencies emerged that lead to an erosion of confidence in the estimated model predictions. For example, estimates of liver cancer in US residents from aflatoxins, DDT, and chlordane were estimated via LNT modeling to be well over one million people/year [285]. Yet the number of liver cancers from all causes, including alcohol ingestion and virus infections, was orders of magnitude lower! These epidemiological validation challenges to LNT modeling predictions were complemented with the discoveries of a cascade of robust adaptive processes that further undercut the theoretical basis of the LNT model, while providing biological support for a threshold dose–response concept. Furthermore, during the late 1970s when the EPA was floating the idea for the LNT model, it also tried to support this position via two complementary approaches: one using the results of epidemiological studies in survivors of the atomic bomb blasts in Japan, while the second was via the use of mutagenicity data using the Ames data. In the case of the atomic bomb exposures, this support became quickly tentative given the nature of the exposures, the dose rates, and their relevance to low-dose exposures in society and the extreme difficulty in teasing out specific radiation exposures as its effects may have been affected by heat, shock, and other confounding factors and the apparent differential effects on different cancer types. The atomic bomb survivor study became more of a research vehicle rather than an environmental risk assessment instrument, forcing the agency to back away from using it as its central perspective to support a community-based linearity policy. A second policy probe put forward by the agency during this period was that of using evidence of linearity in dose–response with Ames mutagenicity strains. The EPA was linking the mechanism of genotoxicity to cancer with the Ames test data as the vehicle. This was also quickly withdrawn as the agency recognized the error of using DNA-deficient strains to support the LNT concept. Such tactics used by the EPA in the late 1970s were to be seen as scientifically amateurish, perhaps the action of a young agency. It was better to formulate a position based on a protectionist philosophy than to be embarrassed publicly on the science.

Much research and debate over the question of cancer risk assessment has focused on whether thresholds for mutagens might exist. Lost in this debate was the key paper of Caspari and Stern [144] that was marginalized by Stern and Muller (see Calabrese [10], Uphoff and Stern [286]). While the threshold debate initially focused on ionizing radiation [287–289], it was soon extended to chemicals [290–302]. During this period of the dose–response concept formulation for mutagens, the Environmental Mutagen Society proposed that mutagens be covered under the Delaney Clause and not be permitted to be added to food. They argued that there was no safe level of exposure since mutagens displayed a linear low-dose relationship. While this was a debate that the society lost, the debate over dose–response, especially for genotoxic agents and genotoxic carcinogens, has continued unabated to the present [112,303–321]. Regulatory agencies, such as EPA, have adhered to the LNT approach for carcinogen risk assessment for the next 40 years and continue to do so. Of interest in this regard was the striking statement of Kenny Crump, a key architect of the LNT multistage model used by the EPA in QRA in the mid-1970s to the present. In a major retrospective, Crump [322] tends to place this intellectual cacophony in the scientific world in perspective. He stated that "quantitative risk assessment, as currently practiced is broken. Despite a huge investment in 'risk research'


ED_002751_00030366-00042

the effort has failed to resolve the shape of the dose response curve for any substance." Crump [322] further stated

> Science is not capable of determining the shape of the dose response at very low doses. Hypotheses regarding the existence or non-existence of thresholds are beyond the ability of science to resolve... Continuing to expend energy and time debating the irresoluble issue of thresholds, and base decision rules on it, are a detriment to fashioning a logical and workable comprehensive approach to risk assessment.

The argument of Crump is a statistical one. He notes that various research groups have reported on the occurrence of threshold and supported their conclusions by the use of a hockey stick dose–response model [316,323,324]. According to Crump [322], the best that can be said about the threshold dose–response in such cases is that it fits the data significantly better than a perfectly linear dose–response. Despite this factual conclusion, this assumption does not prove nor even imply that the true dose–response has a threshold. Crump [322] carried this argument further by assuming that the slope of the dose–response could, in fact, be quite shallow, yet still not a threshold. In this sense, he argued that this type of evaluation supports his conclusion that it is impossible to say which model is correct.

This statistical argument of Crump's has potential theoretical value when dealing with threshold dose–responses that also do not display a U-shaped or HDR. If an HDR were to be demonstrated, it would constitute proof that a threshold not only existed but had been reasonably demonstrated. This would be especially the case when the mechanism of the HDR was established.

## OPEN LETTER

The concept of the dose–response has a long and controversial history in the field of toxicology and risk assessment. The controversy is not simply a modern one but one that emerged as soon as the first formal dose–response model was proposed in the 1880s. In fact, the controversies that swirl around the dose–response in the form of linearity, threshold, and hormesis can trace many of the issues back to the roots of the initial disputes. This chapter traced this history and its evolution. One of the further issues is that I have been at the center of the dose–response debate over the past two decades, leading the resurgence of the HDR in toxicology and the broader biomedical sciences. When one takes on both a leadership role and a scientific role in the development of a scientific concept, it can be challenging to be balanced in the assessment and in this case the writing of this chapter. The editor was quite clear to me that this chapter had to be about dose–response and not simply about hormesis. It was a challenge that I took seriously and looked forward to being successful with.

While I became very involved with the hormesis topic from 1990 to the present, I was first introduced to this concept as an undergraduate in a plant physiology class doing a laboratory exercise on the dose–response of a synthetic plant growth inhibitor with the peppermint plant. Unexpectedly, our research team observed that the growth inhibitor seemed to stimulate the plant growth. After the course ended, I followed up on this observation and worked with a professor to determine if the effects were reproducible. With multiple experiments and many hundreds of peppermint plants; later, I was able to conclude that the findings were reproducible and showed an inverted U-shaped dose–response with a low-dose stimulation and a high-dose inhibition. The magnitude of the stimulation was always modest, being about 30%–60% greater than the controls. Since these initial findings were in soil, I did further work to see if the effects could be shown to occur in hydroponics. Similar reproducible findings occurred. The findings were published in the journal *Physiological Plantarum*. The dose–response was simply called a low-dose stimulation and high-dose inhibition as I had yet to hear of the term hormesis, even though I was to learn later that it had been created in the early 1940s. AQ29

I put aside the peppermint work and went to graduate school hoping to become an insecticide toxicologist. Over the next 20 years or so, I become very involved in the toxicology and risk assessment communities, serving on numerous major committees, including a series of NAS SDWCs, the Air Cabin Safety Committee that lead to the banding of smoking in airplanes, and an Institute of Medicine committee. I wrote nearly a dozen singly authored books, most of which dealt with the issue of dose–response. In rereading these books, my views were very much in line with the views of the federal agencies, supporting thresholds for noncarcinogens and linearity for carcinogens. In fact, this is the way that I taught my toxicology and risk assessment courses. My views on dose–response were completely *mainstream* and never challenging the status quo.

I was reintroduced to the topic of hormesis in 1985 when I received a brochure for a conference sponsored by the Electric Power Research Institute. I was invited to participate in the meeting by the late Leonard Sagan, with a paper addressing chemical examples of hormesis. While the paper was completed, it was presented by a graduate student, as I was unable to attend due to the birth of my second son. During the 1990s, my interest continued on the topic of hormesis, with an openness to discovering whether this phenomenon was very general and biologically significant. I was far from sure on this matter until the near to the end of the 1990s, when at last I had seen enough data within a sound evaluative framework that I finally concluded that there was something very significant going on with the hormesis concept. At that point, I threw myself fully into the study of hormesis, pretty much dropping all other previously funded areas. My scientific intuition told me that this could be very important to give it the highest priority. I have done this ever since and it was a good decision.

Despite this commitment to the study of hormesis, I did not give up my capacity to be objective, to see weaknesses in experiments, and to try to find ways to gain better scientific insights. Our work in this area is characterized by the publication of numerous articles in a broad range of high-level journals, with strong independent peer-reviewed activities. What I have learned is that it has been far harder to pass peer reviews on topics related to hormesis than all my previous areas of research. There is often an extra set of reviewers and a more skeptical associate editor that seem to raise the


ED_002751_00030366-00043

publication bar far higher for things hormetic. While frustrating, this has been good in many ways as the finally accepted manuscripts are typically of higher quality. During the course of these years of hormesis focus, my work and I personally have been the object of much criticism and debate. Much of the criticism has been of excellent quality and has been helpful to improve future efforts. However, there are other criticisms that are clearly ideologically, based on a fear that hormesis may harm environmental regulations. Such criticisms often include personal attacks and unfounded accusations that hormesis is simply a ploy used by industry to weaken standards. We have shown from the early days of the hormesis revolution that the hormetic response could be beneficial, harmful, or neither. In fact, Baldwin and I were the first to publish this, a view that is now widely accepted. We have also reported cases in which the hormetic response was replaced by a triphasic dose–response, with damage occurring at the lowest levels of exposure. The point is that it is not hard to be objective, when one has been trained to be objective and where one has lived this way. This is the fun of science. The only way to gain solid insight is to follow the data. I have done this over 40 years since receiving my PhD, and I have tried to do this in this chapter on dose–response. Nonetheless, I have an informed perspective and I share it. It may not be fully correct and I suspect that my understandings and views will change with new data and assessments. Yet this chapter is my honest attempt to give the reader my best insight into the dose–response and how the toxicology community came to its understandings and whether they have been correct or wrong and why.

## QUESTIONS

**3.1** Could the inverted U-shaped dose–responses observed for some endocrine disrupting agents be examples of hormesis? Explain how and why you think that this might be the case or why not.

**3.2** What are the risk assessment implications of the observation that latency of tumor development is inversely related to dose?

**3.3** What are the toxicological advantages and disadvantages of having an animal model for the chronic bioassay to have a low or negligible background tumor incidence?

**3.4** How does the concept of dose–response synergy differ depending upon whether the synergy occurs above the threshold or below the threshold in the hormetic zone?

**3.5** In toxic tort litigation, epidemiological response twofold greater than the control group is not accepted as showing causality. Why is this the case and should there be exceptions to it, and what might they be and why?

**3.6** Are their areas of toxicology and clinical medicine that do not show a dose–response? If so, what would they be? How would this phenomenon be explained?

## KEYWORDS

Dose–response, Threshold, Linearity, Hormesis, Risk assessment, Biphasic, U-shaped, J-shaped

## REFERENCES


1. National Research Council (NRC). *Science and Decisions: Advancing Risk Assessment*. Committee on Improving Risk Analysis Approaches used by EPA. December 2, 2008; 36 p. AQ30
2. Environmental Protection Agency (EPA). An examination of EPA risk assessment principles and practices. Prepared by members of the Risk Assessment Task Force (EPA/100/B/001) March, Washington, DC, 2004.
3. Calabrese EJ, Baldwin LA. Chemical hormesis: Its historical foundations as a biological hypothesis. *Hum Exp Toxicol* 2000; 19(1):2–31.
4. Calabrese EJ, Baldwin LA. The marginalization of hormesis. *Hum Exp Toxicol* 2000; 19(1):32–40.
5. Calabrese EJ, Baldwin LA. Radiation hormesis: Its historical foundations as a biological hypothesis. *Hum Exp Toxicol* 2000; 19:41–75.
6. Calabrese EJ, Baldwin LA. Radiation hormesis: Part 2—The demise of a legitimate hypothesis. *Hum Exp Toxicol* 2000; 19:76–84.
7. Calabrese EJ, Baldwin LA. Tales of two similar hypotheses: The rise and fall of chemical and radiation hormesis. *Hum Exp Toxicol* 2000; 19:86–97.
8. Calabrese EJ. Getting the dose–response wrong. Why hormesis marginalized and the threshold model accepted. *Arch Toxicol* 2009; 83:227–247.
9. Calabrese EJ. The road to linearity: Why linearity at low doses became the basis for carcinogen risk assessment. *Arch Toxicol* 2009; 83:203–225.
10. Calabrese EJ. Muller's Nobel Prize lecture: When ideology prevailed over science. *Toxicol Sci* 2012; 126(1):1–4.
11. Calabrese EJ. Hormesis and the Salk vaccine. *Dose Response* 2012; AQ31
12. Fisher RA. The correlation between relatives on the supposition of Mendelian inheritance. *Philos Trans R Soc Edinburgh* 1918; 52:399–433.
13. Koch R. Ueber Desinfection. Mitlheil a. d. Kaiserl. Gesundheitsamte Vol (1). (Cited in Chick and Martin, 1908) 1881.
14. Chick H. An investigation of the laws of disinfection. *J Hyg* 1908; 8(1):92–158.
15. Chick H, Martin CJ. The principles involved in the standardization of disinfectants and the influence of organic matter upon germicidal value. *J Hyg* 1908; 8(5):654–697.
16. Lee ER, Gilbert CA. On the application of the mass law to the process of disinfection—Being a contribution to the "mechanistic theory" as opposed to the "vitalistic theory". *J Phys Chem* 1918; 22(5):348–372.
17. Eaton DL. Scientific judgment and toxic torts—A primer in toxicology for judges and lawyers. *12 J.L. & POL'Y 5*, 2003; 15. AQ32
18. Coulter HL. *Homoeopathic Medicine*. Washington, DC: American Foundation of Homoeopathy, 1972; 73pp.
19. Perrin J. *Brownian Movement and Molecular Reality* (trans. F Soddy). London, U.K.: Taylor & Francis Group. (This is a translation of a paper that appeared in the *Annales de Chimie et de Physique*, 8me Series, 1909). 1910; 93pp.
20. Wolf P. Eighteen Theses. Illustrating the principles of homeopathy, according to their true sense and scientific acceptation, addressed to the friends and opponents of that method of cure (translated from the German, by CF Matlack, MD). In: Association of Homoeopathic Physicians (ed.) *Miscellanies on Homoeopathy*. Philadelphia, PA: WLJ Kiderlen & Co., 1839.
21. Coulter HL. *Divided Legacy: The Conflict between Homoeopathy and the American Medical Association*. Berkeley, CA: North Atlantic Books, 1982; 552pp.




ED_002751_00030366-00044

22. Bernard C. *Lecons sur le Diabete et la Glycogenese Animale*. France, Paris: Librarie J. B. Bailliere et Fils, 1877; 132pp.
23. Schulz H. Zur Lehre von der Arzneiwirdung. *Virchows Archiv Pathol Anatom Physiol Klin Med* 1887; 108:423–445.
24. Schulz H. Uber Hefegifte. *Pflugers Archiv Physiol Menschen Tiere* 1888; 42:517–541.
25. Bohme H. 1986. Hugo Schulz (8/6/1853–7/13/1932). His life and work. Dissertation. Freien University of Berlin, Berlin, Germany, 1986.
26. Crump T. NIH Library Translation (NIH-98-134). Contemporary medicine as presented by its practitioners themselves, Leipzig, 1923:217–250, Hugo Schulz. *Nonlinearity Biol Toxicol Med* 2003; 1:295–318.
27. Bloedau CV. *General Medical Central* 1884; 93:1362 (Cited in Schulz, 1885).
28. Schulz H. About the treatment of cholera with veratrine. *German Med Weekly Pap* 1885; 11:99.
29. Calabrese EJ. Toxicology rewrites its history and rethinks its future: Giving equal focus to both harmful and beneficial effects. *Environ Toxicol Chem* 2011; 30(12):2658–2673.
30. Kotschau K. The effect of small doses with reference to the Arndt-Schulz law and homeopathy, Part 2. *Deut Med Wochenschrift* 1928; 54:1586–1588.
31. Kotschau K. The effect of small doses with reference to the Arndt-Schulz law and the homeopathy, Part 2. *Deut Med Wochenschrift* 1928; 54:1631–1632.
32. Schulz H. 1918. *Rudolf Arndt and the Fundamental Law of Biology*. Greifswald, L. Bamberg, Germany.
33. Wels P. The life time work of Hugo Schulz. *Naunyn-Schmiedebergs Archiv Exper Pathol Pharmakol* 1933; 170:744–757.
34. Martius-Rostock F. The Arndt-Schulz axiom. *The Munich Med Weekly News* 1923; 70(31):1–4.
35. Clark AJ. *Mode of Action of Drugs on Cells*. London, U.K.: Arnold, 1933; 298pp.
36. Clark AJ. *Handbook of Experimental Pharmacology*. Berlin, Germany: Verlig Von Julius Springer, 1937.
37. Dannenberg H. Yeast fermentation: On the question of the validity of the Arndt-Schulz rule. *Naunyn-Schmiedebergs Arch Exper Pathol Pharmakol* 1930; 154:211–221.
38. Branham SE. The effects of certain chemical compounds upon the course of gas production by Baker's yeast. *J Bacteriol* 1929; 18:247–284.
39. Calabrese EJ. Key studies to support cancer risk assessment questioned. *Environ Mol Mutagen* 2011; 52(8):595–606.
40. Calabrese EJ. Muller's Nobel lecture on dose–response for ionizing radiation: Ideology or science? *Arch Toxicol* 2011; 85(12):1495–1498.
41. Duggar BM. Aureomycin: A product of the continuing search for new antibiotics. *Ann N Y Acad Sci* 1948; 51:177–181.
AQ33 42. Rahn O. The rate of fermentation (Chapter 5). In: *Physiology of Bacteria*. Philadelphia, PA: P. Blakiston's Son & Co., Inc., 1932; pp. 137–140.
43. Hofmann P. Ueber die Gültigkeit des Arndt-Schulz'schen Grundgesetzes bei der Wirkung von Bakteriengiften. Dissertation, tierärztl. Fakultät, München, Germany, 1922.
44. Townsend CO. The correlation of growth under the influence of injuries. *Ann Botany* 1897; 11:509–532.
45. Hueppe F. *Principles of Bacteriology* (translated from the German by E.O. Jordan). Chicago, IL: The Open Court Publishing Company, 1896; 457pp.
AQ34 46. Calabrese EJ, Dhawan G. The role of x-rays in the treatment of gas gangrene: A historical assessment. *Dose–Response* 2012; 10(4)~~(In Press)~~. DOI:10.2203/dose-response.12–016. Calabrese.
47. Calabrese EJ, Calabrese V. ~~2012~~, ~~Low~~ dose radiation therapy (LD-RT) ~~reduces arthritis symptoms via induction of~~ an anti-inflammatory phenotype. *Int J Radiat Biol* 2012; ~~(in press)~~.
48. Duggar BM. *Plant Physiology, with Special Reference to Plant Production*. New York: Macmillan, 1911; 516pp.
49. Salle AJ. 1939. *Fundamental Principles of Bacteriology*. New York: McGraw-Hill Book Company, 1939; pp. 166–197.
50. Clifton CE. *Introduction to Bacterial Physiology*. New York: McGraw-Hill, 1957; pp. 317–338.
51. Lamanna C, Mallette MF. *Basic Bacteriology: Its Biological and Chemical Background*, 3rd edn. Baltimore, MD: Lippincott Williams & Wilkins Company, 1965; 1001pp.
52. Marshall MS, Hrenoff AK. Bacteriostasis. *J Infect Dis* 1937; 61:42–54.
53. Luckey TD. *Ionizing Radiation and Hormesis*. Boca Raton, FL: CRC Press, 1980.
54. Luckey TD. *Radiation Hormesis*. Boca Raton, FL: CRC Press, 1991; 306pp.
55. Richards HM. The effect of chemical irritation on the economic coefficient of sugar. *Bull Torrey Bot Club* 1899; 26:463–479.
56. Richards HM. On the nature of response to chemical stimulation. *Science* 1910; 31:52–62.
57. Falk IS. The role of certain ions in bacterial physiology. A review (Studies of Salt Action, VIII). *Abstr Bacteriol* 1923; 7:33–50, 87–105, 133–147.
58. Hotchkiss M. The influence of various salts upon the growth of bacterium communis. PhD thesis. Yale University, New Haven, CT, 1922.
59. Hotchkiss M. Studies on Salt Action: VI. The stimulating and inhibitive effect of certain cations upon bacterial growth. *J Bacteriol* 1923; 8:141–162.
60. Shackell LF. The relation of dosage to effect. II. *J Pharmacol Exp Ther* 1925; 15:275–288.
61. Shackell LF, Williamson W, Deitchmann MM et al. The relation of dosage to effect. *J Pharmacol Exp Ther* 1924/1925; 23/24:53–65.
62. Cushny AR. *The Secretion of the Urine*. London, U.K.: Longmans, Green & Company, 1926; 288pp.
63. Foster RHK. Standardization of safety margin. *J Pharmacol Exp Ther* 1939; 65(1):1–17.
64. Taylor LS. *Radiation Protection Standards*. CRC Monotopics Series. Cleveland, OH: Chemical Rubber Company Press, 1971; 110pp.
65. Lehman AJ, Fitzhugh OG. 100-Fold margin of safety. *Assoc Food Drug Off, Quart Bull* 1953; 17(2):33–35.
66. Flexner A. Medical education in the United States and Canada. A Report to the Carnegie Foundation for the Advancement of Teaching, New York, 1910; 887pp.
67. Berliner H. *A System of Scientific Medicine*. New York: Tauistock Publication, 1985; 190pp.
68. Clark AJ. The reaction between acetyl choline and muscle cells. *J Physiol* 1926; 61:530–546.
69. Clark AJ. The historical aspects of quackery, Part 2. *Brit Med J* 1927; 960.
70. Clark AJ. *Applied Pharmacology*. Philadelphia, PA: P. Blakiston's Son & Co., 1927; 678pp.
71. Bliss CI. The comparison of dosage-mortality data. *Ann Appl Biol* 1935; 22:307–333.
72. Bliss CI. Estimating the dosage-mortality curve. *J Econ Entomol* 1935; 25:646–647.
73. Bliss CI. The calculation of the dosage-mortality curve. *Ann Appl Biol* 1935; 22:134–167.
74. Bliss CI. The toxicity of poisons applied jointly. *Ann Appl Biol* 1939; 26:585–615.




ED_002751_00030366-00045

75. Bliss CI. Biometry in the service of biological assay. *Ind Eng Chem* 1941; 13:84–88.
76. Bliss CI. The calculation of microbial assays. *Bacteriol Rev* 1956; 20:243–258.
77. Bliss CI. Some principles of bioassay. *Am Sci* 1957; 45:449–466.
78. Bliss CI, Packard C. Stability of the standard dosage-effect curve for radiation. *Am J Roentgenol Rad Ther* 1941; 46:400–404.
79. Bliss CI, McKeen C. Biological assay. *Ann Rev Physiol* 1943; 5:479–539.
80. Gaddum JH. *Methods of Biological Assay Depending on the Quantal Response*. London, U.K.: H.M. Stationery Office, 1933; 46pp.
81. Southam CM, Ehrlich J. Effects of extracts of western red-cedar heartwood on certain wood-decaying fungi in culture. *Phytopathology* 1943; 33:517–524.
82. Whittemore FG Jr. The National Committee on Radiation Protection, 1928–1960: From professional guidelines to government regulation. Thesis. Department of History of Science, Harvard University, Cambridge, MA, 1986.
83. Jolly C. Thresholds of uncertainty: Radiation and responsibility in the fallout controversy. PhD dissertation. Oregon State University, Corvallis, OR, 2003; 591pp.
84. Mutscheller A. Physical standards of protection against roentgen ray dangers. *Am J Roentgenol Radiat Ther* 1925; 13:65–70.
85. Mutscheller A. Safety standards of protection against x-ray danger. *Radiology* 1928; 10:468–476.
86. Sievert R. Einige untersuchungen uber vorricht ungen zum schutz gegen roentgenstrahlen. *Acta Radiol* 1925; 4:61.
87. Barclay AE, Cox S. Radiation risks of the roentgenologist. *Am J Roentgenol Radiat Ther* 1928; 19:551–561.
88. Muller HJ. Artificial transmutation of the gene. *Science* 1927; 66:84–87.
89. Muller HJ. The problem of genetic modification. Verhandlungen des V. Internationalen Kongresses fur Vererbungswissenschaft (Berlin, 1927) in Zeitschrift fur inductive abstammungs- und Vererbungslehre. *Suppl Band* 1928; 1:234–260.
90. Stadler LJ. Some genetic effect of x-rays in plants. *J Hered* 1930; 21:3–19.
91. Hutchinson GE. The biogeochemistry of aluminum and of certain related elements (concluded). *Quart Rev Biol* 1943; 18(4):331–363.
92. Hutchinson GE. The influence of the environment. *Proc Natl Acad Sci USA* 1964; 51(5):930–934.
93. Dinman DB. Non-concept of no threshold—Chemicals in environment. *Science* 1972; 4021:495–497.
94. Webb JL. *Enzyme and Metabolic Inhibitors*, Vol. 3. New York: Academic Press, 1966; 1028pp.
95. Cornfield J, Rai K, Van Ryzin J. Procedures for assessing risk at low levels of exposure. *Arch Toxicol* 1980; 3:295–303.
96. Schaeffer D. Thresholds for carcinogenesis and their significance to medical practice. *Med Hypotheses* 1983; 10:175–184.
97. Pollycove M, Feinendegen LE. Radiation-induced versus endogenous DNA damage: Possible effect of inducible protective responses in mitigating endogenous damage. *Hum Exp Toxicol* 2003; 22(6):290–306.
98. Green DE, Vande Zande HD. Universal energy principle of biological systems and the unity of bioenergetics. *Proc Natl Acad Sci USA* 1981; 78(9):5344–5347.
99. Schaeffer DJ, Janardan KG, Kerster HW. Threshold estimation from the linear dose–response model: Method and radiation data. *Environ Manage* 1981; 5(6):515–520.
100. Schaeffer DJ, Kerster HW, Janardan KG. The low dose extrapolation problem: A review and a new model. *Am J Math Manage Sci* 1982; 2(3):223–251.
101. Janardan KG, Kerster HW, Schaeffer DJ. Biological applications of the Lagrangian poisson distribution. *BioScience* 1979; 29(10):599–602.
102. Schaeffer DJ, Janardan KG, Kerster HW, Clarke ACM. Statistically estimated free energies of chromosome aberration production from frequency data. *Biometrical J* 1983; 25(3):275–282.
103. Koch R. A threshold concept of environmental Pollutants. *Chemosphere* 1983; 12(1):17–21.
104. Friedman L. Problems of evaluating the health significance of the chemicals present in foods. In: *Pharmacology and the Future of Man* (*Proceedings of the Fifth International Congress on Pharmacology*), Vol. 2. Karger: Basel, Switzerland, 1973; pp. 30–41.
105. Claus G. Environmental carcinogens: Is there a threshold of exposure? *Clin Toxicol* 1974; 7(5):497–508.
106. Jukes TH. A quantitative evaluation of estrogens, including DES, in the diet. *Am Stat* 1982; 36(3):273–277.
107. Preussmann R. The problem of thresholds in chemical carcinogenesis, some views on theoretical and practical aspects. *J Cancer Res Clin Oncol* 1980; 97:1–14.
108. Mohr U, Hilfrich H. Effect of a single dose of N-diethylnitrosamine on the rat kidney. *J Natl Cancer Inst* 1972; 49:1729–1731.
109. Williams GM, Iatropoulos MJ, Jeffrey AM. Mechanistic basis for nonlinearities and thresholds in rat liver carcinogenesis by the DNA-reactive carcinogens 2-acetylaminofluorene and diethylnitrosamine. *Toxicol Pathol* 2000; 28(3):388–395.
110. Williams GM, Iatropoulos MJ, Jeffrey AM. Thresholds for the effects of 2-acetylaminofluorene in rat liver. *Toxicol Pathol* 2004; 32:85–91.
111. Williams GM, Iatropoulos MJ, Jeffrey AM. Thresholds for DNA-reactive (genotoxic) organic carcinogens. *Toxicol Pathol* 2005; 18:69–77.
112. Parry JM, Jenkins GJS, Haddad F et al. In vitro and in vivo extrapolations of genotoxin exposures: Consideration of factors which influence dose–response thresholds. *Mutat Res* 2000; 464:53–63.
113. Claus G, Bolander K, Krisko I. Man-made chemical mutagens in the natural environment: An evaluation of hazards. *Studia Biophys* (*Berlin*) 1975; 50:123–136.
114. Fahmy OG, Fahmy MJ. The genetic effects of the biological alkylating agents with reference to pesticides. *Ann N Y Acad Sci* 1969; 160(1):228–243.
115. Ames BN. The detection of chemical mutagens with enteric bacteria. In: *Chemical Mutagens: Principles and Methods for Their Detection*. New York: Plenum Press, 1971; pp. 267–282.
116. Slikker Jr W, Andersen ME, Bogdanffy MS et al. Dose-dependent transition in mechanisms of toxicity. *Toxicol Appl Pharmacol* 2004; 201:203–225.
117. Slikker Jr W, Andersen ME, Bogdanffy MS et al. Dose-dependent transitions in mechanisms of toxicity: Case studies. *Toxicol Appl Pharmacol* 2004; 201:226–294.
118. Monticello TM, Swenberg JA, Gross EA et al. Correlation of regional and nonlinear formaldehyde-induced nasal cancer with proliferating populations of cells. *Cancer Res* 1996; 56:1012–1022.
119. Belinsky SA, Walker VE, Maronpot RR et al. Molecular dosimetry of DNA adduct formation and cell toxicity in rat nasal-mucosa following exposure to the tobacco specific nitrosamine 4-(N-methyl-N-nitrosamino)-1-(3-pyridyl)-1-butanone and their relationship to induction of neoplasia. *Cancer Res* 1987; 47(22):6058–6065.



ED_002751_00030366-00046

120. Rozman KK, Kerecsen L, Viluksela MK et al. A toxicologist's view of cancer risk assessment. *Drug Metab Rev* 1996; 28(1 and 2):29–52.
121. Gaddum JH. Lognormal distributions. *Nature* 1945; 156:463.
122. Tritscher AM, Goldstein JA, Portier CJ et al. Dose–response relationships for chronic exposure to 2,3,7,8-tetrachlorodibenzo-*p*-dioxin in a rat tumor promotion model: Quantification and immunolocalization of CYP 1A1 and CYP 1A2 in the liver. *Cancer Res* 1992; 52:3436–3442.
123. Waddell WJ, Crooks NH, Carmichael PL. Correlation of tumors with DNA adducts from methyl eugenol and tamoxifen in rats. *Toxicol Sci* 2004; 79:38–40.
124. Waddell WJ. Threshold of carcinogenicity of flavors. *Toxicol Sci* 2002; 68:275–279.
125. Waddell WJ. Thresholds in chemical carcinogenesis: What are animal experiments telling us? *Toxicol Pathol* 2003; 31(3):260–262.
126. Waddell WJ. Threshold for carcinogenicity of N-nitrosodiethylamine for esophageal tumors in rats. *Food Chem Toxicol* 2003; 41:739–741.
127. Waddell WJ. Threshold of carcinogenicity in the ED01 study. *Toxicol Sci* 2003; 72:158–163.
128. Waddell WJ. Rebuttal to Haseman. *Toxicol Pathol* 2003; 31:712–713.
129. Waddell WJ. Letters to the editor—Reply. *Toxicol Sci* 2003; 74:485–486.
130. Waddell WJ. Letters to the editor—Reply. *Toxicol Sci* 2003; 74:487–488.
131. Waddell WJ. Analysis of thresholds for carcinogenicity. *Toxicol Lett* 2004; 149:415–419.
132. Waddell WJ. Comparisons of thresholds for carcinogenicity on linear and logarithmic dosage scales. *Hum Exp Toxicol* 2005; 24:325–332.
133. Waddell WJ. Critique of dose response in carcinogenesis. *Hum Exp Toxicol* 2006; 25(7):413–436.
134. Waddell WJ. History of dose response. *J Toxicol Sci* 2010; 35(1):1–8.
135. Crump KS, Clewell HJ. Letters to the Editor. *Toxicol Sci* 2003; 74:485–488.
136. Andersen ME, Conolly RB, Gaylor DW. Letters to the editor—Letter. *Toxicol Sci* 2003; 74:486–487.
137. Lutz WK. Letters to the editor. *Toxicol Sci* 2003; 75:223–225.
138. Haseman JJK. Response to Waddell & Rozman. *Toxicol Pathol* 2003; 31(6):715–716.
139. Enomoto M. Thresholds in chemical carcinogenesis: What are animal experiments telling us? *Toxicol Pathol* 2003; 31:573–574.
140. Rozman KK. Rebuttal to Haseman. *Toxicol Pathol* 2003; 31:714.
141. National Academy of Sciences (NAS)/National Research Council (NRC). The biological effects of atomic radiation: A report to the public. Washington, DC: NAS/NRC, 1956.
142. Lewis EB. Leukemia and ionizing radiation. *Science* 1957; 125:965–972.
143. DuShane G. Loaded dice. *Science* 1957; 125:964.
144. Caspari E, Stern C. The influence of chronic irradiation with gamma-rays at low dosages on the mutation rate in *Drosophila melanogaster*. *Genetics* 1948; 33:75–95.
AQ35 145. Muller HJ. The production of mutations. Nobel Lecture, 1946. Nobleprize.org (http:www.nobelprize.org/nobel-prizes/medicine/laureates/1946).
146. Crow JF. Quarreling geneticists and a diplomat. *Genetics* 1995; 140:421–426.
147. Henry HF. Is all nuclear radiation harmful? *J Am Med Assoc* 1961; 176(8):671–675.
148. Henahan JF. Whatever happened to the Cranberry Crisis. *The Atlantic Monthly* 1977; 239:26–36.
149. National Academy of Sciences (NAS)/National Research Council (NRC). *The Effects on Populations of Exposure to Low Levels of Ionizing Radiation*. Washington, DC: Division of Medical Sciences, 1972.
150. National Academy of Sciences Safe Drinking Water Committee (NAS SDWC). *Drinking Water and Health*. Washington, DC: National Academy of Sciences, 1977.
151. Fisher JC, Hollomon JH. A hypothesis for the origin of cancer foci. *Cancer* 1951; 4(5):916–918.
152. Muller HJ. Radiation damage to the genetic material. *Sci Prog* 1951; 7:93–94.
153. Iversen S, Arley N. On the mechanism of experimental carcinogenesis. *Acta Pathol Microbiol Scand* 1950; 27:773–803.
154. Nordling CO. A new theory on the cancer-inducing mechanism. *Br J Cancer* 1953; 7:68–72.
155. Driver HE, White INH, Butler WH. Dose–response relationships in chemical carcinogenesis—Renal mesenchymal tumors induced in the rat by single dose dimethylnitrosamine. *Br J Exp Pathol* 1987; 68(2):133–143.
156. Ogura K, Magae J, Kawakami Y, Koana T. Reduction in mutation frequency by very low-dose gamma irradiation of *Drosophila melanogaster* germ cells. *Radiat Res* 2009; 171(1):1–8.
157. Luckey TD, Venugopal B, Hutcheson D. *Heavy Metal Toxicity Safety and Hormology*. New York: Academic Press, 1975; 120pp.
158. Elliott KC. *Is A Little Pollution Good For You? Incorporating Societal Values into Environmental Research*. London, U.K.: Oxford University Press, 2011; 246pp.
159. Thayer KA, Melnick R, Burns K et al. 2005. Fundamental flaws of hormesis for public health decisions. *Environ Health Perspect* 2005; 113:1271–1276.
160. Thayer KA, Melnick R, Huff J et al. Hormesis: A new religion? *Environ Health Perspect* 2006; 114:A632–A633.
161. Axelrod D, Burns K, Davis D et al. Hormesis—An inappropriate extrapolation from the specific to the universal. *Int J Occup Environ Health* 2004; 10:335–339.
162. Sagan LA. On radiation, paradigms, and hormesis. *Science* 1989; 245:574–621.
163. Wolff S. Are radiation-induced effects hormetic. *Science* 1989; 245:575–621.
164. Szabadi E. A theoretical model of two functionally opposite receptor populations. *Br J Pharmacol* 55(2):311; *Proceedings of the B. P. S.* (September 15–17, 1975) Edinburgh, Scotland, 1975; 311pp.
165. Szabadi E. Model of 2 functionally antagonistic receptor populations activated by same agonist. *J Theor Biol* 1977; 69:101–112.
166. Dale HH. On some physiological actions of ergot. *J Physiol (London)* 1906; 34(3):163–206.
167. Alfonzo MJ, de Becemberg IL, de Villaroel SS et al. Two opposite signal transducing mechanisms regulate a G-protein-coupled guanylyl cyclase. *Arch Biochem Biophys* 1998; 350(1):19–25.
168. Rovati GE, Nicosia S. Lower efficacy—Interaction with an inhibitory receptor or partial agonism. *Trends Pharmacol Sci* 1994; 15(5):140–144.
169. Rovati GE, Nicosia S. An alternative model for bell-shaped concentration–response curves—Reply. *Trends Pharmacol Sci* 1994; 15(9):321–322.
170. Jarv J. A model of nonexclusive binding of agonist and antagonist on G-protein coupled receptors. *J Theor Biol* 1995; 175(4):577–582.


ED_002751_00030366-00047

171. Accomazzo MR, Cattaneo S, Nicosia S et al. Bell-shaped curves for prostaglandin-induced modulation of adenylate cyclase: Two mutually opposing effects. *Eur J Pharmacol* 2002; 454:107–114.
172. Marmot MG, Rose G, Shipley MJ et al. Alcohol and mortality—A U-shaped curve. *Lancet* 1981; 1:580–583.
173. Stebbing ARD. Hormesis—The stimulation of growth by low-levels of inhibitors. *Sci Total Environ* 1982; 22(3):213–234.
174. Stebbing ARD. A theory for growth hormesis. *Mutat Res* 1998; 403(1–2):249–258.
175. Stebbing A. *A Cybernetic View of Biological Growth: The Maia Hypothesis*. New York: Cambridge University Press, 2011; 436pp.
176. Samson L, Cairns J. A new pathway for DNA in *Escherichia coli*. *Nature* 1977; 267:281–283.
177. ~~Olivier~~ G, Bodycote J, Wolff S. Adaptive response of human-lymphocytes to low concentrations of radioactive thymidine. *Science* 1984; 223(4636):594–597.
178. Murry CE, Jennings RB, Reimer KA. Preconditioning with ischemia—A delay of lethal cell injury in ischemic myocardium. *Circulation* 1986; 74:1124–1136.
179. Calabrese EJ, Blain R. The occurrence of hormetic dose response in the toxicological literature, the hormesis database: An overview. *Toxicol Appl Pharmacol* 2005; 202(3):289–301.
180. Calabrese EJ, Blain RB. Hormesis and plant biology. *Environ Pollut* 2009; 157(1):42–48.
181. Calabrese EJ, Blain RB. The hormesis database: The occurrence of hormetic dose responses in the toxicological literature. *Regul Toxicol Pharmacol* 2011; 61(1):73–81.
182. Calabrese EJ, Baldwin LA. Defining hormesis. *Hum Exp Toxicol* 2002; 21(2):91–97.
183. Calabrese EJ. Converging concepts: Adaptive response, preconditioning, and the Yerkes-Dodson Law are manifestations of hormesis. *Ageing Res Rev* 2008; 7(1):8–20.
184. Calabrese EJ. Hormesis: Why it is important to toxicology and toxicologists. *Environ Toxicol Chem* 2008; 27(7):1451–1474.
185. Mattson MP. Hormesis defined. *Ageing Res Rev* 2008; 7(1):1–7.
186. Calabrese EJ, Baldwin LA. The frequency of U-shaped dose responses in the toxicological literature. *Toxicol Sci* 2001; 62(2):330–338.
187. Calabrese EJ, Baldwin LA. Hormesis: U-shaped dose responses and their centrality in toxicology. *Trends Pharmacol Sci* 2001; 22(6):285–291.
188. Calabrese EJ, Baldwin LA. U-shaped dose responses in biology, toxicology, and public health. *Annu Rev Public Health* 2001; 22:15–22.
189. Calabrese EJ, Baldwin LA. The hormetic dose–response model is more common than the threshold model in toxicology. *Toxicol Sci* 2003; 71(2):246–250.
190. Calabrese EJ, Baldwin LA. Chemotherapeutics and hormesis. *Crit Rev Toxicol* 2003; 33:305–353.
191. Calabrese EJ, Staudenmayer JW, Stanek III EJ et al. Hormesis outperforms threshold model in National Cancer Institute antitumor drug screening database. *Toxicol Sci* 2006; 94(2):368–378.
192. Calabrese EJ, Stanek III EJ, Nascarella MA et al. Hormesis predicts low-dose responses better than threshold models. *Int J Toxicol* 2008; 27(5):369–378.
193. Calabrese EJ, Hoffmann GR, Stanek EJ et al. Hormesis in high-throughput screening of antibacterial compounds in *E. coli*. *Hum Exp Toxicol* 2010; 29(8):667–677.
194. Gaylor DW. The $ED_{01}$ study: Summary and conclusions. *J Environ Pathol Toxicol* 1980; 3:179–183.
195. Cairns T. $ED_{01}$ study: Introduction, objectives and experimental design. *J Environ Pathol Toxicol* 1980; 3:1–7.
196. Staffa JA, Mehlman MA. Innovations in cancer risk assessment ($ED_{01}$ study). *J Environ Pathol Toxicol* (Special Issue) 1980; 3:1–246.
197. Bruce RD, Carlton WW, Ferber KH et al. (Members of the Society of Toxicology $ED_{01}$ Task Force). Re-examination of the $ED_{01}$ study—Adjusting for time on study. *Fundam Appl Toxicol* 1981; 1:67–80.
198. Calabrese EJ. Evidence that hormesis represents an "overcompensation" response to a disruption in homeostasis. *Ecotoxicol Environ Saf* 1999; 42:135–137.
199. Calabrese EJ. Overcompensation stimulation: A mechanism for hormetic effects. *Crit Rev Toxicol* 2001; 31(4–5):425–470.
200. Hilbert DW, Swift DM, Detling JK et al. Relative growth rates and the grazing optimization hypothesis. *Oecologia (Berlin)*, 1981; 51:14–18.
201. Calabrese EJ, Mattson MP. Hormesis provides a generalized quantitative estimate of biological plasticity. *J Cell Commun Signal* 2011; 5:25–38.
202. Begley S. *Train Your Mind, Change Your Brain*. New York: Balantine Books, 2007; 304pp.
203. Bradshaw AD. Evolutionary significance of phenotypic plasticity in plants. *Adv Genet* 1965; 13:115–155.
204. Carrel A. Artificial activation of the growth in vitro of connective tissue. *J Exp Med* 1913; 17:14–19.
205. Calabrese EJ. Historical foundations of wound healing and its potential for acceleration: Dose–response considerations. *Wound Rep Reg* ~~2012; in press~~.
206. Gaddum JH. The pharmacologist of Edinburgh. *Annu Rev* 1962; 2:1–10.
207. Calabrese EJ. Hormesis and pharmacology. In: Hacker M, Bachmann K, Messer W (eds.). *Pharmacology Principles and Practice*. Burlington, MA: Academic Press, 2009; pp. 75–102.
208. Stephenson RP. A modification of receptor theory. *Br J Pharmacol* 1956; 11:379–393.
209. Ariens EJ. Affinity and intrinsic. *Arch Intern Pharmacodyn* 1954; 99:273–278.
210. Del Castillo J, Katz B. The identity of intrinsic and extrinsic acetylcholine receptors in the motor end-plate. *Proc R Soc B Biol Sci* 1957; 146(924):357–361.
211. Del Castillo J, Katz B. A comparison of acetylcholine and stable depolarizing agents. *Proc R Soc B Biol Sci* 1957; 146(924):362–368.
212. Del Castillo J, Katz B. Interaction at end-plate receptors between different choline derivatives. *Proc R Soc B Biol Sci* 1957; 146(924):369–380.
213. Ariens EJ, Van Rossum JM, Simonis AM. Affinity, intrinsic activity and drug interactions. *Pharmacol Rev* 1957; 9:218–236.
214. Furchgott RF. The pharmacology of vascular smooth muscle. *Pharmacol Rev* 1955; 7(2):183–265.
215. Okpako DR. Dual action of histamine on guinea pig lung vessels. *Br J Pharmacol* 1972; 45(2):311–321.
216. Eyre P. Histamine H2-receptors in sheep bronchus and cat trachea—Action of burimamide. *Br J Pharmacol* 1973; 48(2):321–323.
217. Kehoe J. Ionic mechanisms of a 2-component cholinergic inhibition in aplysia neurons. *J Physiol (London)* 1972; 225(1):85–114.
218. Ascher P. Inhibitory and excitatory effects of dopamine on aplysia neurons. *J Physiol* 1972; 225:173–209.




ED_002751_00030366-00048

219. Gerschen HM, Paupardi D. Ionic mechanisms and receptor properties underlying responses of molluscan neurons to 5-hydroxytryptamine. *J Physiol (London)* 1974; 243(2):427–456.
220. De Groat WC, Lalley PM. Interaction between picrotoxin and 5-hydroxytryptamine in superior cervical ganglion of cat. *Br J Pharmacol* 1973; 48(2):233–244.
221. Brimble MJ, Wallis DI. Histamine H1 and H2-receptors at a ganglionic synapse. *Nature* 1973; 246(5429):156–158.
222. Ariens EJ, Simonis AM, Van Rossum JM. Drug–receptor interaction: Interaction of one or more drugs with different receptor systems. In: Ariens EJ (ed.). *Molecular Pharmacology*. New York: Academic Press, 1964; pp. 287–393.
223. Jarv J. An alternative model for model-shaped concentration response curve. *Trends Pharmacol Sci* 1994; 15:321.
224. Leff P. Theoretical treatment of one-agonist-2-receptor systems. *Trends Pharmacol Sci* 1994; 15(9):320–321.
225. Barlow RB. Problems associated with the partiality of a partial agonist. *Trends Pharmacol Sci* 1994; 15:320.
226. Quirk SJ, Gannell JE, Funder, JW. Adrenocorticoid-dependent alpha-lactalbumin synthesis in rat mammary gland explants—Antagonist studies. *Clin Exp Pharmacol Physiol* 1986; 13(3):233–239.
227. Quirk SJ, Gannell JE, Fullerton MJ, Funder JW. Specificity and mechanism of biphasic action of glucocorticoids on alpha-lactalbumin production by rat mammary gland explants. *Endocrinology* 1986; 118(3):909–914.
228. Jarv J, Rinken A. Muscarinic acetylcholine receptors. In: Hucho, F (ed.). *Neurotransmitter Receptors*. New York: Elsevier, 1993; pp. 214–217.
229. Jarv J, Toomela T, Karelson E. Dual effect of carbachol on muscarinic receptor. *Biochem Mol Biol Intern* 1993; 30:649–654.
230. Jarv J, Hedlund B, Bartfai T. Kinetic-studies on muscarinic antagonist-agonist competition. *J Biol Chem* 1980; 225(7):2649–2651.
231. Leuchenko A, Bruck J, Sternberg PW. Regulatory modules that generate biphasic signal response in biological systems. *System Biol* 2004; 1:139–148.
232. Quirk SJ, Funder JW. Steroid receptors, and the generation of closely coupled/biphasic dose response curves. *J Steriod Biochem* 1988; 30:9–15.
233. Goldstein BD, Henifin MS. Reference guide on toxicology. In: *Reference Manual on Scientific Evidence*, 2nd edn. Federal Judicial Center 2000; pp. P401–P438.
234. Rhomberg LR, Goodman JE, Haber LT et al. Linear low-dose extrapolation for noncancer health effects is the exception, not the rule. *Crit Rev Toxicol* 2011; 41(1):1–19.
235. Enstrom JE. Fine particulate air pollution and total mortality among elderly Californians, 1973–2002. *Inhalation Toxicol* 2005; 17(14):803–816.
236. Glende EA. Carbon tetrachloride-induced protection against carbon-tetrachloride toxicity—Role of liver microsomal drug-metabolizing system. *Biochem Pharmacol* 1972; 21(12):1697–1702.
237. Mehendale HM. Tissue repair: An important determinant of final outcome of toxicant-induced injury. *Toxicol Pathol* 2005; 33(1):41–51.
238. Mehendale HM. Once initiated, how does toxic tissue injury expand? *Trends Pharmacol Sci* 2012; 33(4):200–206.
239. Yoshikawa H. Preventive effect of pretreatment with low dose of metals on the acute toxicity of metals in mice. *Ind Health* 1970; 8:184–191.
240. Calabrese EJ, Bachmann KA, Bailer AJ et al. Biological stress response terminology: Integrating the concepts of adaptive response and preconditioning stress within a hormetic dose–response framework. *Toxicol Appl Pharmacol* 2007; 222:122–128.
241. Calabrese EJ. *Age and Susceptibility to Toxic Substances*. New York: John Wiley & Sons, 1986; 312pp.
242. Calabrese EJ. *Pollutants and High Risk Groups*. New York: John Wiley & Sons, 1978; 283pp.
243. Calabrese EJ. Historical blunders: How toxicology got the dose–response relationship half right. *Cell Mol Biol* 2005; 51:643–654.
244. Rödel F, Frey B, Gaipl U et al. Modulation of inflammatory immune reactions by low-dose ionizing radiation: Molecular mechanisms and clinical application. *Curr Med Chem* 2012; 19:1741–1750.
245. Trott KR. Therapeutic effects of low radiation doses. *Strahlenther Onkol* 1994; 170:1–12.
246. Trott KR, Kamprad F. Estimation of cancer risks from radiotherapy of benign diseases. *Strahlenther Onkol* 2006; 182:431–436.
247. Arenas M, Gil F, Gironella M et al. Anti-inflammatory effects of low-dose radiotherapy in an experimental model of systemic inflammation in mice. *Int J Radiat Oncol Biol Phys* 2006; 66:560–567.
248. Arenas M, Gil F, Gironella M et al. Time course of anti-inflammatory effect of low-dose radiotherapy: Correlation with TGF-$\beta_1$ expression. *Radiother Oncol* 2008; 86:399–406.
249. Weng L, Williams RU, Vieira PL et al. The therapeutic activity of low-dose irradiation on experimental arthritis depends on the induction of endogenous regulatory T cell activity. *Ann Rheum Dis* 2010; 69:1519–1526.
250. Hildebrandt G, Radlingmayr A, Rosenthal S et al. Low-dose radiotherapy (LD-RT) and the modulation of iNOS expression in adjuvant-induced arthritis in rats. *Int J Radiat Biol* 2003; 79:993–1001.
251. Hildebrandt G, Seed MP, Freemantle CN et al. Effects of low dose ionizing radiation on murine chronic granulomatous tissue. *Strahlenther Onkol* 1998; 174:580–588.
252. Hildebrandt G, Seed MP, Freemantle CN et al. Mechanisms of the anti-inflammatory activity of low-dose radiation therapy. *Int J Radiat Biol* 1998; 74:367–378.
253. Nakatsukasa H, Tsukimoto M, Ohshima Y et al. Suppressing effect of low-dose gamma-ray irradiation on collagen-induced arthritis. *Radiat Res* 2008; 49:381–389.
254. Nakatsukasa H, Tsukimoto M, Tokunaga A et al. Repeated γ irradiation attenuates collagen-induced arthritis via up-regulation of regulatory T cells but not by damaging lymphocytes directly. *Radiat Res* 2010; 174:313–324.
255. Schaue D, Jahns J, Hildebrandt G, Trott K-R. Radiation treatment of acute inflammation in mice. *Int J Radiat Biol* 2005; 81:657–667.
256. Frey B, Gaipl US, Sarter K et al. Whole body low dose irradiation improves the course of beginning polyarthritis in human TNF-transgenic mice. *Autoimmunity* 2009; 42:346–348.
257. Rödel F, Hantschel M, Hildebrandt G et al. Dose-dependent biphasic induction and transcriptional activity of nuclear factor kappa B (NF-κB) in EA.hy.926 endothelial cells after low-dose x-irradiation. *Int J Radiat Biol* 2004; 80:115–123.
258. Rödel F, Schaller U, Schultze-Mosgau S et al. The induction of TGF-β1 and NF-κB parallels a biphasic time course of leukocyte/endothelial cell adhesion following low-dose x-irradiation. *Strahlenther Onkol* 2004; 180:194–200.
259. Rödel F, Keilholz L, Herrmann M et al. Radiobiological mechanisms in inflammatory disease of low-dose radiation therapy. *Int J Radiat Biol* 2007; 83:357–366.



ED_002751_00030366-00049

260. Rödel F, Hofmann D, Auer J et al. The anti-inflammatory effects of low-dose radiation therapy involves a diminished CCL20 chemokine expression and granulocyte/endothelial cell adhesion. *Strahlenther Onkol* 2008; 184:41–47.
261. Rödel F, Keilholz L, Herrmann M et al. Activator protein 1 shows a biphasic induction and transcriptional activity after low dose x-irradiation in EA.hy.926 endothelial cells. *Autoimmunity* 2009; 42:343–345.
262. Rödel F, Frey B, Capalbo G et al. Discontinuous induction of x-linked inhibitor of apoptosis in EA.hy.926 endothelial cells in linked to NF-κB activation and mediates the anti-inflammatory properties of low-dose ionising-radiation. *Radiat Oncol* 2010; 97:346–351.
263. Rödel F, Kamprad F, Sauer R et al. Low-dose radiotherapy: Molecular and functional aspects. *Strahlenther Onkol* 2002; 178:1–9.
264. Roedel F, Kley N, Beuscher HU et al. Anti-inflammatory effect of low-dose x-irradiation and the involvement of a TGF-β1-induced down-regulation of leukocyte/endothelial cell adhesion. *Int J Radiat Biol* 2002; 78:711–719.
265. DiChiara MR, Kiely JM, Gimbrone MA Jr et al. Inhibition of E-selecting gene expression by transforming growth factor beta in endothelial cells involves coactivator integration of Smad and nuclear factor kappaB-mediated signals. *J Exp Med* 2000; 192:695–704.
266. Hooker A, Bhat M, Day TK et al. The linear no-threshold model does not hold for low-dose ionizing radiation. *Radiat Res* 2004; 162(4):447–452.
267. Choi VWY, Yum EHW, Konishi T et al. Triphasic low-dose response in Zebrafish embryos irradiated by microbeam protons. *J Radiat Res* 2012; 53:475–481.
268. Ames BN, Gold LS. Paracelsus to parascience: The environmental cancer distraction. *Mutat Res Fundam Mol Mech Mutagen* 2000; 447(1):3–13.
269. Calabrese EJ, Baldwin LA. Does exceeding the MTD increase or decrease the cancer incidence in rodent studies—A testable hypothesis. *Drug Metab Rev* 1992; 24(4):421–424.
270. Gold LS, Slone TH, Ames BN. What do animal cancer tests tell us about human cancer risk? Overview of analyses of the carcinogenic potency database. *Drug Metab Rev* 1998; 30(2):359–404.
271. Spencer WP, Stern C. Experiments to test the validity of the linear R-dose mutations frequency in *Drosophila* at low dosage. *Genetics* 1948; 33:43–74.
272. Druckrey H. Quantitative Grundlagen der Krebserzeugung. *Klin Wochenschr* 1943; 22:532–534.
273. Druckrey H, Küpfmüller K. Quantitative analyse der krebsentstehung. *Z Naturforsch* 1948; 3b:254–266.
274. Druckrey H. Quantitative aspects in chemical carcinogenesis. In: Truhaut R (ed.). *Potential Carcinogenic Hazards from Drugs*. UICC Monograph Series, Vol. 7. Berlin, Germany: Springer-Verlag, 1967; 60pp.
275. Druckrey H. Pharmacological approach to carcinogenesis. In: Weistenholme G, O'Connor M (eds.). *CIBA Foundation Symposium on Carcinogenesis—Mechanisms of Actions*. Boston, MA: Little, Brown and Co, 1959; pp. 110–130.
276. Suss R, Kinzel V, Scribner JD. *Cancer: Experiments and Concepts*. Berlin, Germany: Springer-Verlag, 1973; 50pp.
277. Yanysheva NY, Antomonov YG. Predicting the risk of tumor occurrence under the effect of small doses of carcinogens. *Environ Health Perspect* 1976; 13:95–99.
278. Jones HB, Grendon A. Environmental factor in the origin of cancer and estimation of the possible hazard to man. *Food Cosmet Toxicol* 1975; 13:251–268.
279. Enterline PE. Pitfalls in epidemiological research. *J Occup Med* 1976; 18(3):150–156.
280. OSHA. Rules on the identification, classification and regulation of potential occupation carcinogens. January 24, 1980. *Fed Regist* 1980; 45(15):5002–5296.
281. Guess HA, Hoel DG. The effect of dose on cancer latency period. *J Environ Pathol Toxicol* 1977; 1:279–286.
282. Albert RE, Altshuler B. Considerations relating to the formulation of limits for unavoidable population exposures to environmental carcinogens. In: Sander CL, Busch RH, Ballou JE, Mahlum DD (eds.). *Radionuclide Carcinogenesis (Proceedings of the Twelfth Annual Hanford Biology Symposium*, Richland, WA), AEC Symposium Series No. 29, Conference 720505. NTIS: Springfield, VA, 1973; pp. 233–253.
283. Albert RE, Altshuler B. Assessment of environmental carcinogen risks in terms of life shortening. *Environ Health Perspect* 1976; 13:91–94.
284. National Academy of Sciences (NAS). *Principles for Evaluating Chemicals in the Environment*. Washington, DC: *National Academy of Sciences*, 1975.
285. Calabrese EJ. *Methodological Approaches to Deriving Environmental and Occupational Health Standards*. New York: John Wiley & Sons, 1978; 402pp.
286. Uphoff DE, Stern C. The genetic effects of low intensity in irradiation. *Science* 1949; 109:609–610.
287. Brues AM. Critique of mutational theories of carcinogenesis. *Acta Unio Internationalis Contra* 1960; 16(2):415–417.
288. Brues AM. Radiation thresholds. *Arch Environ Health* 1971; 22:690–691.
289. Brues AM, Sacher GA. The significance of time–dose relationships in carcinogenesis. *Cancer Res* 1951; 11(4):240.
290. Drake JW, Abrahamson S, Crow JF et al. Environmental mutagenic hazards. *Science* 1975; 187:503–514.
291. Drake JW. 1978. Some guidelines for determining maximum permissible levels of chemical mutagens. In: Flamm WG, Mehlman MA (eds.). *Advances in Modern Toxicology*, Vol. 5—Mutagenesis. New York: Hemisphere Publishing Corporation, 1978; 926pp.
292. Freese E. Thresholds in toxic, teratogenic, mutagenic, and carcinogenic effects. *Environ Health Perspect* 1973; 6:171–178.
293. Frayssinet C. The principle of a threshold dose in chemical carcinogenesis. *Food Addit Contam* 1984; 1(2):89–94.
294. Hatch TF. Thresholds: Do they exist? *Arch Environ Health* 1971; 22:687–689.
295. Henschle D. New approaches to a definition of threshold values for irreversible toxic effects. *Arch Toxicol* 1974; 32(1):63–67.
296. Mantel N, Heston WE, Gurian JM. Thresholds in linear dose–response models for carcinogenesis. *J Natl Cancer Inst* 1961; 27:203–215.
297. Potter VR. How is an optimum environment defined? *Environ Res* 1969; 2:476–487.
298. Rall DP. Thresholds? *Environ Health Perspect* 1978; 22:163–165.
299. Stokinger HE. Concepts of thresholds in standards setting—Analysis of concept and its application to industrial air limits (TLVS). *Arch Environ Health* 1972; 25(3):153–157.
300. Falk HL. Biologic evidence for the existence of thresholds in chemical carcinogenesis. *Environ Health Perspect* 1978; 22:167–170.
301. Upton AC. Environmental standards for ionizing radiation—Theoretical basis for dose–response curves. *Environ Health Perspect* 1983; 52:31–39.



ED_002751_00030366-00050

302. Ziehlhuis RL. Permissible limits for occupational exposure to toxic agents—Discussion on differences in approach between U.S. and U.S.S.R. *Int Arch Arbeitmed* 1974; 33(1):1–13.
303. Zeise L, Wilson R, Crouch EAC. Dose–response relationships for carcinogens: A review. *Environ Health Perspect* 1987; 73:259–308.
304. Zito R. Low doses and thresholds in genotoxicity: From theories to experiments. *J Exp Clin Cancer Res* 2001; 20(3):315–325.
305. Weisburger JH, Williams GM. The distinction between genotoxic and epigenetic carcinogens and implication for cancer risk. *Toxicol Sci* 2000; 57:4–5.
306. Speit G, Autrup H, Crebelli R et al. Thresholds in genetic toxicology—Concluding remarks. *Mutat Res* 2000; 464:149–153.
307. Slob W. Thresholds in toxicology and risk assessment. *Int J Toxicol* 1999; 18:259–268.
308. Purchase IFH, Auton TR. Thresholds in chemical carcinogenesis. *Regul Toxicol Pharmacol* 1995; 22:199–205.
309. Parry JM. Reflections on the implications of thresholds of mutagenic activity for the labeling of chemicals by the European Union. *Mutat Res* 2000; 464:155–158.
310. Neumann H-G. Risk assessment of chemical carcinogens and thresholds. *Crit Rev Toxicol* 2009; 39(6):449–461.
311. Madle S, von der Hude W, Broschinski L et al. Threshold effects in genetic toxicity: Perspective of chemicals regulation in Germany. *Mutat Res* 2000; 464:117–121.
312. Lovell DP. Dose–response and threshold-mediated mechanisms in mutagenesis: Statistical models and study design. *Mutat Res* 2000; 464:87095.
313. Kondo S. Evidence that there are threshold effects in risk of radiation. *J Nuclear Sci Technol* 1999; 36(1):1–9.
314. Jenkins GJS, Doak SH, Johnson GE et al. Do dose response thresholds exist for genotoxic alkylating agents? *Mutagenesis* 2005; 20(6):389–398.
315. Jin M, Dewa Y, Kawai M et al. The threshold dose for liver tumor promoting effects of dicyclanil in ICR mice. *J Toxicol Sci* 2010; 35(1):69–78.
316. Johnson GE, Doak SH, Griffiths SM et al. Nonlinear dose–response of DNA-reactive genotoxins: Recommendations for data analysis. *Mutat Res Genet Toxicol Environ Mutagen* 2009; 678:95–100.
317. Henderson L, Albertini S, Aardema M. Thresholds in genotoxicity responses. *Mutat Res* 2000; 464:123–128.
318. Hengstler JG, Bogdanffy MS, Bolt HM et al. Challenging dogma: Thresholds for genotoxic carcinogens? The case of vinyl acetate. *Annu Rev Pharmacol Toxicol* 2003; 43:485–520.
319. Fry RJM. The questions of thresholds for carcinogenesis. *Cancer Invest* 1989; 7:299–300.
320. Elmore E, Lao X-Y, Ko M et al. Neoplastic transformation in vitro induced by low doses of 232 MeV protons. *Int J Radiat Biol* 2005; 81:291–298.
321. Elmore E, Lao X-Y, Kapadia R et al. Threshold-type dose response for induction of neoplastic transformation by 1 GeV/nucleon iron ions. *Radiat Res* 2009; 171:764–770.
322. Crump KS. Use of threshold and mode of action in risk assessment. *Crit Rev Toxicol* 2011; 41(8):637–650.
323. Pottenger LH, Carmichael N, Banton MI et al. ECETOC workshop on the biological significance of DNA adducts: Summary of follow-up from an expert panel meeting. *Mutat Res Genet Toxicol Environ Mutagen* 2009; 678:152–157.
324. Steenland K, Mannetje A, Boffetta P et al. Pooled exposure-response and risk assessment for lung cancer in 10 cohorts of silica-exposed workers: An IARC multicentre study. *Cancer Causes Control* 2001; 12:773–784.
325. Calabrese EJ. Hormesis: Principles and applications for pharmacology and toxicology. *Am J Pharmacol Toxicol* 2008; 3(1):56–68.
326. Clark DH. *Alfred Joseph Clark (1885–1941). A Memoir.* Glastonbury, England: C & J Clark Ltd, 1985; 61pp.
327. Sukata T, Uwagawa S, Ozaki K et al. Detailed low-dose study of 1,1-BIS(*p*-chlorophenyl)-2,2,2-trichloroethane carcinogenesis suggests the possibility of a hormetic effect. *Int J Cancer* 2002; 99:112–118.



ED_002751_00030366-00051

## AUTHOR QUERIES

[AQ1] All occurrences of "dose response (s)/dose-response(s)" have been changed to "dose–response (s)" Please check if okay.

[AQ2] Please provide alternate standard source for Figures 3.1, 3.2, 3.4, 3.5, 3.14, 3.15, and 3.19, if appropriate.

[AQ3] The word "and" has been changed to "on". Please check if okay.

[AQ4] Please check if edit to the sentence starting "The first was..." is okay.

[AQ5] All occurrences of "Avagardro's" have been changed to "Avogadro's". Please check if okay.

[AQ6] Please provide complete details for the source line of Figures 3.6, 3.8, 3.9, 3.13 and 3.16 through 3.18, and also, add the same in the reference list.

[AQ7] Please check if the inserted closing parenthesis in sentence starting "Despite these challenges..." is okay.

[AQ8] Please check if edit to the sentence starting "There was no..." is okay.

[AQ9] Please check the change of "1977" to "1877" in the caption of Figure 3.14 for correctness.

[AQ10] Please check if edit to the sentence starting "he became quite..." is okay.

[AQ11] Please check "World War" for clarity.

[AQ12] Please provide the expansion of the acronym "DMN," if appropriate.

[AQ13] Please check if the inserted expansion for "NNK" is okay.

[AQ14] Please check if edit to the sentence starting "That the threshold…" is okay.

[AQ15] Please check if edit to the sentence starting "This committee would…" is okay.

[AQ16] Please check if "Erhlich" can be changed to "Ehrlich" here.

[AQ17] Please provide the expansion of the acronym "SOT," if appropriate.

[AQ18] Please provide the significance of "*" in the artwork of Figures 3.24 and 3.25.

[AQ19] Please check if edit to the sentence starting "The study was..." is okay.

[AQ20] Please check if edit to section heading is okay.

[AQ21] Please check if edit to the sentence starting "The responses of..." is okay.

[AQ22] Please check if edit to the sentence starting "It was often reported..." is okay.

[AQ23] All occurrences of "goosencoid" have been changed to "goosecoid". Please check if okay.

[AQ24] All occurrences of "heterogenicity" have been changed to "heterogeneity". Please check if okay.

[AQ25] All occurrences of "heterogeneity-LNT" have been changed to ""heterogeneity-based LNT". Please check if okay.

[AQ26] Please check the author name "Branham" does not match with Ref. [199].

[AQ27] Please check the author name "Druckrey" does not match with Ref. [276].

[AQ28] Please check if the inserted expansion for "OSHA" is okay.

[AQ29] Please check if edit to the sentence starting "With multiple experiments..." is okay.

[AQ30] Please provide publisher details for Ref. [1].

[AQ31] Please provide complete details for Refs. [11,13].

[AQ32] Please provide page number for Refs. [17,20,69].

[AQ33] Please provide editor details for Refs. [42,104,115,233].

[AQ34] Please update Refs. [46,47,205].

[AQ35] Please provide accessed date and more details if any for Ref. [145].



ED_002751_00030366-00052

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 1/4/2019 2:36:32 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: FW: follow on Senate Testimony

---

**From:** Bliss, Joe (Rounds) <Joe_Bliss@rounds.senate.gov>
**Sent:** Friday, January 4, 2019 9:35 AM
**To:** Edward Calabrese <edwardc@schoolph.umass.edu>
**Subject:** RE: follow on Senate Testimony

Ed,

Thank you for sharing. The record for the hearing has officially closed several weeks ago.

Thanks
Joe Bliss

---

**From:** Edward Calabrese <edwardc@schoolph.umass.edu>
**Sent:** Friday, January 4, 2019 7:28 AM
**To:** Bliss, Joe (Rounds) <Joe_Bliss@rounds.senate.gov>
**Subject:** follow on Senate Testimony

Dear Joe:

The attached paper was just published this week. It relatedly directly to my presentation and to some of the follow up questions that I was asked to address.
I would like to have this paper entered into the record and shared with the entire Senate committee. Please note that I have checked on the North American
Members of the editorial board and all are notable leaders in their areas. Thus, I believe that this journal is of very high standing.

Sincerely,

Ed Calabrese

Message

**From**: Dominguez, Alexander [dominguez.alexander@epa.gov]
**Sent**: 4/13/2018 3:41:34 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: Academics List Revised
**Attachments**: Academics.xlsx

Attached is the revised list of academics – omitting any that were on Stephen's list. Just a few gaps of information I could not find, and one email address at the very bottom I can find no person to attach to.

---

**From:** Dominguez, Alexander
**Sent:** Wednesday, April 11, 2018 4:22 PM
**To:** Woods, Clint <woods.Clint@epa.gov>
**Subject:** Academics

Attached is the excel doc with a list of academics.

**Alex Dominguez**
Policy Analyst to the Principal Deputy
Office of Air and Radiation
U.S. Environmental Protection Agency

# Academic Contacts

| First Name | Last Name | Email Address |
|---|---|---|
| Jerome | Arnett | Ex. 6 Personal Privacy (PP) |
| Robert | Bailey | |
| Dallas | Baker | dallas.baker@neel-schaffer.com |
| Keith | Belton | kebelton@iu.edu |
| Richard | Belzer | rbbelzer@post.harvard.edu |
| Alex | Berezow | Ex. 6 Personal Privacy (PP) |
| Daniel | Botkin | dan@danielbbotkin.com \|\| danielbotkin@rcn.com |
| William | Briggs | matt@wmbriggs.com |
| Dan | Byers | Dbyers@USChamber.com |
| Edward | Calabrese | edwardc@schoolph.umass.edu |
| Mark | Campbell | campbell@usna.edu |
| Alan | Carlin | |
| Oren | Cass | Ex. 6 Personal Privacy (PP) |
| Bruce | Copley | bruce.copley@exxonmobil.com |
| Tony | Cox | Ex. 6 Personal Privacy (PP) |
| Judith | Curry | Ex. 6 Personal Privacy (PP) |

| Highest Degree Earned | Occupation | Link |
|---|---|---|
| M.D. | | |
| | Correspondent, Reason | Bio |
| MBA, Mississippi College | Director of Environmental Services, Neel-Schaffer | Linkedin |
| Ph.D., (public policy) George Washington University | Director, Manufacturing Policy Initiative | Bio |
| Ph.D., Harvard University | President, Regulatory Checkbook; Independent Consulting in Regulatory Policy, Economics, and Risk Analysis | House Science Committee 2017 Testimony |
| Ph.D., (microbiology) University of Washington | | Bio |
| Ph.D., (plant ecology) Rutgers University | Professor Emeritus in the Department of Ecology, Evolution, and Marine Biology at the University of California, Santa Barbara | Bio |
| Ph.D., (statistics) Cornell University | Policy Advisor, Heartland Institute | CV |
| M.S., (soil science) North Carolina State University | Senior Policy Director, U.S. Chamber og Commerce;s Global Energy Institute | Bio |
| Ph.D. (physiology.toxicology), University of Massachusetts at Amherst, MA | Professor, University of Massachusetts at Amherst, MA | CV |
| Ph.D., Johns Hopkins University | Professor, U.S. Naval Academy | USNA Directory |
| Ph.D., (economics) Massachusetts Institute of Technology | | Bio |
| J.D., Harvard Law School | Senior Fellow, Manhattan Institute | Bio |
| Ph.D., (risk analysis) Massachusetts Institute of Technology | ExxonnMobil Biomedical Sciences President, Cox Associates | CV |
| Ph.D., (geophysical sciences) University of Chicago | President, Climate Forecast Applications Network | CV |

| Column1 |
| --- |
| |
| |
| |
| |
| |
| |
| |
| |
| |
| |
| |
| |
| |
| |
| |

| | | |
|---|---|---|
| Susan | Dudley | sdudley@gwu.edu |
| Don | Easterbrook | don.easterbrook@www.edu |
| Peter | Felker | pmf@chem.ucla.edu |
| Barb | Glenn | barb@nasda.org |
| Teresa | Gorman | tagorman@mindspring.com |
| Laurence | Gould | lgould@hartford.edu |
| John | Graham | grahamjd@indiana.edu |
| William | Happer | happer@princeton.edu |
| Michael | Honeycutt | Michael.Honeycutt@tceq.texas.gov |
| Walt | Hufford | whufford@talismanusa.com |
| Jason | Johnston | jjohnston@virgina.edu |
| Jonathan | Lesser | |
| Richard | Lindzen | rlindzen@mit.edu |
| Fred | Lipfert | Ex. 6 Personal Privacy (PP) |
| Randall | Lutter | randall.lutter@virginia.edu \| rl4bh@virginia.edu \| Ex. 6 Personal Privacy (PP) |
| Matthew | Malkan | malkan@astro.ucla.edu |
| Gary | Marchant | Gary.Marchant@asu.edu |
| Roger | McClellan | Ex. 6 Personal Privacy (PP) |
| Mike | McKenna | |

| | | |
|---|---|---|
| M.S. Massachusetts Institute of Technology | Director, GW Regulatory Studies Center & Distinguished Professor of Practice Trachtenberg School of Public Policy & Public Administration | Directory |
| Ph.D | Professor Emeritus of Geology at Western Washington University. | |
| Ph.D. (chemical physics), California Institute of Technology | Professor, University of California, Los Angeles | |
| Ph.D., (ruminant nutrition) University of Kentucky | CEO, NASDA | Bio |
| | | |
| Ph.D., (physics) Temple University | Professor, University of Hartdford | Bio |
| Ph.D., (urban and public affairs) Carnegie-Mellon University | Dean, Indeana University School of Public and Environmental Affairs | Bio |
| Ph.D., (physics) Princeton University | Professor Emeritus, Princeton University | Bio |
| | Director, Toxicology Division, TCEQ | |
| | Director of Government and Regulatory Affairs, Repsol USA | Bio |
| Ph.D (economics), University of Michigan | Professor, University of Virginia School of Law | UVA Directory |
| Ph.D., (economics) University of Washington | President, Continental Economics | CV |
| Ph.D., (applied mathematics) Harvard university | Professor Emeritus, Massachusetts Institute of Technology | Bio |
| | Environmental Consultant | |
| Ph.D. (economics), Cornell University | Professor of Public Policy, University of Virginia | CV |
| Ph.D (astronomy), Caltech | Professor, University of California, Los Angeles | UCLA Directory |
| J.D., Harvard Law School | Professor of Law, Arizona State University | Bio |
| DVM, Washington State University | Advisor, Inhilation Toxicology & Human Health Risk Analysis | CV |
| MPA., George Mason University | President, MWR Strategies | Bio |

| | | |
|---|---|---|
| Henry | Miller | Henry.Miller@stanford.edu |
| Alan | Moghissi | amoghiss@gmu.edu |
| Suresh | Moolgavkar | smoolgavkar@exponent.com |
| Kevin | Neyland | Ex. 6 Personal Privacy (PP) |
| Steve | Packham | spackham@utah.gov \| steven.packham@utah.edu |
| Theresa | Pugh | Ex. 6 Personal Privacy (PP) |
| David | Schoenbrod | dschoenbrod@nyls.edu |
| Roger | Stough | rstough@gmu.edu |
| Stanley | Trimble | trimble@geog.ucla.edu |
| Richard | Trzupek | rtrzupek@trinityconsultants.com |
| Kirby | Tyndall | kirby,tyndall@pbwllc.com |
| George | Wolff | gwolff@airimprovement.com |
| S. Stanley | Young | young@niss.org |
| David | Zorn | Ex. 6 Personal Privacy (PP) |
| Benjamin | Zycher | benjamin.zycher@aei.org \| benzycher@zychereconomics.com |

| | | |
|---|---|---|
| M.D., University of California, San Diego | Fellow, Hoover Institution at Standford university | Bio |
| Ph.D., (physical chemistry) Karlsruhe Institute of Technology | Associate Director of International Center for Regulatory Science at George Mason University | Bio |
| Ph.D., (mathematics) Johns Hopkins University | Senior Fellow & Principal Scientist, Exponent | Bio |
| | | |
| Ph.D., (medical psychology) University of Oregon medical School | Toxicologist, Utah Department of Environmental Quality | Directory |
| BA, (political science/history) Trinity University | Consultant | CV |
| LL.B., Yale University | Trustee Professor of Law, New York Law School | Bio |
| Ph.D., (geography and environmental engineering) Johns Hopkins University | Professor, George Mason University | Bio |
| Ph.D. (population and settlement geography), University of Georgia | Professor Emeritus, University of California, Los Angeles | UCLA Directory |
| | Principal Consultant, Trinity Consultants | |
| Ph.D | Senior Consulting Toxicologist, Pastor Behling & Wheeler | |
| Ph.D., (environmental sciences) Rutgers University | Principal Scientist, Air Improvement Resource, Inc. | Bio |
| Ph.D., (statistics and genetics), North Carolina State University | Fellow, American Statistical Association and the American Association for the Advancement of Science | |
| Ph.D. (economics), George Mason University | Adjunct Professor, George Mason University | Linkedin |
| Ph.D. (economics), University of California, Los Angeles | Senior Fellow, Pacific Research Institute; President of Benjamin Zycher Economics Associates; Resident Scholar. American Enterprise Institute | Bio |

GMU
Directory

Ex. 6 Personal Privacy (PP)

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 1/4/2019 1:35:47 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: FW: follow on Senate Testimony
**Attachments**: Sutou-1.pdf

FYI

---

**From:** Edward Calabrese
**Sent:** Friday, January 4, 2019 8:28 AM
**To:** 'Bliss, Joe (Rounds)' <Joe_Bliss@rounds.senate.gov>
**Subject:** follow on Senate Testimony

Dear Joe:

The attached paper was just published this week. It relatedly directly to my presentation and to some of the follow up questions that I was asked to address.
I would like to have this paper entered into the record and shared with the entire Senate committee. Please note that I have checked on the North American
Members of the editorial board and all are notable leaders in their areas. Thus, I believe that this journal is of very high standing.

Sincerely,

Ed Calabrese

Sutou *Genes and Environment* (2018) 40:26
https://doi.org/10.1186/s41021-018-0114-3

Genes and Environment

COMMENTARY Open Access

# Low-dose radiation from A-bombs elongated lifespan and reduced cancer mortality relative to un-irradiated individuals

Shizuyo Sutou

**Abstract**

The US National Academy of Sciences (NAS) presented the linear no-threshold hypothesis (LNT) in 1956, which indicates that the lowest doses of ionizing radiation are hazardous in proportion to the dose. This spurious hypothesis was not based on solid data. NAS put forward the BEIR VII report in 2006 as evidence supporting LNT. The study described in the report used data of the Life Span Study (LSS) of A-bomb survivors. Estimation of exposure doses was based on initial radiation (5%) and neglected residual radiation (10%), leading to underestimation of the doses. Residual radiation mainly consisted of fallout that poured down onto the ground along with black rain. The black-rain-affected areas were wide. Not only A-bomb survivors but also not-in-the-city control subjects (NIC) must have been exposed to residual radiation to a greater or lesser degree. Use of NIC as negative controls constitutes a major failure in analyses of LSS. Another failure of LSS is its neglect of radiation adaptive responses which include low-dose stimulation of DNA damage repair, removal of aberrant cells via stimulated apoptosis, and elimination of cancer cells via stimulated anticancer immunity. LSS never incorporates consideration of this possibility. When LSS data of longevity are examined, a clear J-shaped dose-response, a hallmark of radiation hormesis, is apparent. Both A-bomb survivors and NIC showed longer than average lifespans. Average solid cancer death ratios of both A-bomb survivors and NIC were lower than the average for Japanese people, which is consistent with the occurrence of radiation adaptive responses (the bases for radiation hormesis), essentially invalidating the LNT model. Nevertheless, LNT has served as the basis of radiation regulation policy. If it were not for LNT, tremendous human, social, and economic losses would not have occurred in the aftermath of the Fukushima Daiichi nuclear plant accident. For many reasons, LNT must be revised or abolished, with changes based not on policy but on science.

**Keywords:** A-bomb survivors, Lifespan, Life Span Study, Linear no-threshold, LNT, Longevity, Residual radiation, Threshold

## Background

Japan is the only country that has sustained a nuclear attack. The weapons dropped in 1945 killed approximately 200,000 people instantaneously. People around the world have been taught for decades since that ionizing radiation is limitlessly hazardous, This supposition is based on a linear no-threshold model (LNT): even the lowest doses of ionizing radiation are hazardous in proportion to their doses, Therefore, it is quite natural that most people think that ionizing radiation from the A-bombs killed people, shortened lifespan, and increased cancer mortality. The Fukushima Daiichi nuclear power plant accident presented an opportunity to study the effects of ionizing radiation on health, after which the author published associated books [1, 2] and papers [3, 4]. Through their composition, it became increasingly clear that LNT has a seriously flawed history [5]. The energy of A-bombs comprised 35% thermal radiation (heat and light), 50% blast energy (pressure shock waves), and 15%

Correspondence: sutou@shujitsu.jp
School of Pharmacy, Shujitsu University, 1-6-1 Nishigawara, Naka-Ku, Okayama-Shi 703-8516, Japan

© The Author(s). 2018 **Open Access** This article is distributed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons license, and indicate if changes were made. The Creative Commons Public Domain Dedication waiver (http://creativecommons.org/publicdomain/zero/1.0/) applies to the data made available in this article, unless otherwise stated.

nuclear radiation [6]. In fact, instantaneous deaths were mostly ascribable to thermal and blast energy (85%), especially in the central area of the blast. People tend to forget that victims of heat and blast were affected in a moment or short period, whereas cancer induction has remained a menace even to the present day. For survivors of today, fear of A-bombs mostly overlaps with fear of cancer. It is less well known that ionizing radiation is not always hazardous. Low-dose radiation sometimes stimulates our defense mechanisms and beneficial (radiation hormesis) [7–10].

Taking these facts into consideration, the effects on lifespan and cancer incidence of A-bomb survivors were reexamined for the present analyses. Letting the data speak, one would hear that low-dose radiation from A-bombs has extended survivor lifespan and reduced cancer mortality on average for A-bomb survivors and not-in-the-city control subjects (NIC). The key to resolving the apparent discrepancy between the received notions and actual data is radiation hormesis and the radiation doses of a hormesis range to which a large fraction of A-bomb survivors and NIC were exposed. Of course, A-bomb survivors who received high doses exhibited shortened lifespan and increased cancer mortality, but they accounted for a minor fraction of all local residents. Therefore, results show that the "average lifespan" was longer and that "average cancer mortality" was reduced overall.

Radiation units such as rem, Sv, and Gy are used here as reference articles use, unless otherwise specified.

## Longer lifespan of some people who were heavily irradiated by ionizing radiation

Reportedly the unhappiest man in the world, Mr. Tsutomu Yamaguchi, was A-bombed at Hiroshima. Later he relocated to Nagasaki, where he survived the second A-bomb attack [11]. He survived the two A-bomb attacks; he might be the happiest man in a sense that more than 70 people were evacuated from Hiroshima to Nagasaki: all except him were killed. More surprising is that the two A-bombs did not shorten his life: he died of stomach cancer at 93.

The Nikkei Shimbun reported on April 5, 2018 that Chairman Sunao Tsuboi of the Japan Confederation of A-Bomb and H-Bomb Sufferers Organizations was selected as an honorary citizen of Hiroshima City. When he was 20, the A-bomb attacks occurred when he was 1.2 km from the epicenter. He is 93 in 2018. He talked to then US President Obama to encourage efforts to abolish nuclear weapons. The occasion on May 27, 2017 was the first visit ever to Hiroshima by a serving president.

When he was 8, Shigeaki Mori was blown into a riverbed from a bridge and injured 2.5 km from the epicenter. He became a historian and discovered that American victims of the A-bomb were present in Hiroshima. His finding was reflected in President Obama's speech, "Why do we come to this place, to Hiroshima? We come to ponder a terrible force unleashed in the not so distant past. We come to mourn the dead, including over 100,000 Japanese men, women and children, thousands of Koreans and a dozen Americans held prisoner." After the speech, a tearful Mori was embraced by Obama. Born in 1937, he has lived longer than the average for Japanese men.

Dr. Don Wiles, Emeritus Professor of Chemistry at Carlton University, Canada, once engaged in extraction of radium from uranium ore for 16 months from 1947. Before the use of cobalt, radium ($20,000/g) encapsulated in a glass tube was used to treat cancer by embedding it into the malignant tissues. The crystallization process used by Marie Curie 50 years before included procedures that were apparently very lax and coarse compared to the present standard: encapsulation was performed with bare hands. Workers ignored the rule to wear rubber gloves because they were slippery. Radiation badges even under the lead shield became black at the daily check. Because radium is similar to calcium in terms of its chemical characteristics, radium was apparently accumulated in Dr. Wiles' bones. Born in 1925, he exhaled about 25 times the legal maximum of radon, a product of radium, at the age of 88. One might assume that he was seriously injured. He stated "About 65 years later, I am still healthy." [12]. These are some examples of increased longevity despite radiation exposure. Are they exceptional?

## A-bomb survivors lifespans are unusually long

Figure 1 presents changes of the number of certificate holders who have been covered by the Law Concerning Relief to Atomic Bomb Survivors. The holders are regarded as A-bomb survivors. Until 1982, holders were more than expected because additional people had been admitted as holders; the holders' superiority in number does not necessarily mean that holders had a long lifespan. After 1982, the expected number became greater than the actual holders because few people were admitted as new and holders were getting steadily older year by year. The mortality ratio of the Japanese that was used to calculate the expected numbers was the average of infants, young people, adults, and elderly people, producing a result that is much less than that of the aged holders. Therefore, the holders' exposure and experience do not necessarily mean that their lifespan is short.

The average lifespan of certificate holders was 80.13 for 2014. The ratio of men to women is not available. The lifespan of Japanese men was 80.21 for 2013 and that for women was 86.61; the average was 83.49.

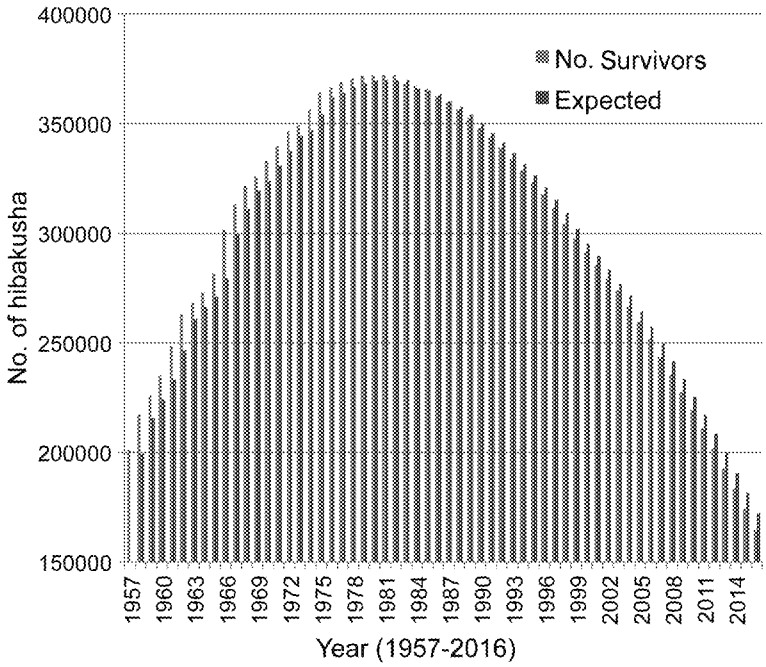



**Fig. 1** Changes of people who have an A-Bomb Survivor's Certificates (Ministry of Health, Labour and Welfare [58] (blue). For example, a total of 183,519 certificate holders in 2014 comprised four classes: 1st class survivors, or direct victims (113,685); 2nd class survivors, or in-city victims who were within areas inside 2 km from the epicenter (42,529); 3rd class survivors, or rescue victims who engaged in rescue activities or physical treatments outside the 2 km areas and who were exposed to residual radiation (20,013); and 4th class survivors, or fetuses of people in one of the above three categories (7292). Their peak number was 372,264 in 1980. Expected numbers (red) were calculated as follows: holders in 1957 were 200,984; the death ratio of the Japanese in 1957 [59] was 0.008275 and 1663 (200,984 × 0.008275) were expected to die and 199,321 (200,984–1663) was the expected number in 1958 (the same hereinafter). Certificate holders are supported financially with six allowances and funeral fees. Some other benefits accrue: they can undergo free health examinations twice a year; and almost all sicknesses are treated at no charge. Patients with illness caused by a nuclear weapon were eligible to receive an allowance of 138,380 yen/m. The health control allowance is 34,030 yen/m. The funeral allowance is 206,000 yen. The total budget for fiscal year 2015 was 393,391,000,000 yen

The life expectancy (for remaining life) at age 80 is 8.61 for men and 8.19 for women. Therefore, the lifespan of A-bomb survivors is expected to be over 88, far exceeding the average. This elongated average lifespan of holders might be ascribable to good medical services offered by the Japanese government. This might have contributed to some degree, but apparently some other important factor has an influence: low-dose radiation stimulates human biological defense mechanisms.

## A-bomb survivors lifespan was statistically shortened

Cologne and Preston investigated the longevity of 120,321 A-bomb survivors [13]. They concluded that "Median life expectancy decreased with increasing radiation dose at a rate of about 1·3 years per Gy, but declined more rapidly at high doses. Median loss of life among cohort members with estimated doses below 1 Gy was about 2 months, but among the small number of cohort members with estimated doses of 1 Gy or more it was 2·6 years. Median loss of life among all individuals with greater-than-zero dose estimates was about 4 months." Almost all readers of the summary sentences above must believe that ionizing radiation from A-bombs was hazardous and that it shortened A-bomb survivors' longevity to a greater or lesser degree. One must nevertheless be alert. The A-bomb survivors lifespan was not necessarily shortened, as described later. When a model cannot explain established facts, not the facts but the model must be wrong. What reasons are there in the discrepancy between actual life elongation and statistical shortening of lifespan? Apparently, three major factors engender wrong conclusions: 1) invalid LNT was promulgated – one never considers life elongation and cancer mortality reduction as effects of radiation; 2) a false assumption (zero exposure-zero risk) in NIC was used by neglecting residual radiation; and 3) radiation hormesis, the idea that low-dose radiation stimulates defense systems, was neglected. These three points are briefly examined before returning to discussion of Cologne and Preston's data [13] later.

## LNT is not based on solid data

### Muller's tenacity to maintain LNT

The origin of LNT dates back to 1927, when Muller found that X-rays induced sex-linked recessive lethality in *Drosophila melanogaster* [14]. This "data-poor/discussion-rich" paper was quite likely to have cleverly circumvented the normal peer review process [15]. Later, he presented related data. Apparent linearity at extremely high doses was extrapolated to lower doses without experimental data. He put forward the proportionality rule, an analog of LNT [16]. Then in 1939, World War II (WWII) broke out. The United States of America (USA) began production of the A-bomb under its Manhattan Project. Radiation effects on living organisms were investigated intensively. He learned of a threshold for positive excess risk in recessive lethality tests of *D. melanogaster* [17]. The US dropped A-bombs on Hiroshima and Nagasaki in 1945. Muller became a Nobel laureate in 1946 for his radiation research. Although he knew of thresholds to damage from radiation, he declared in his Nobel Prize lecture that there was "no escape from the conclusion that there is no threshold dose" [18].

### Oil industries felt uneasy about nuclear energy and took over the National Academy of Sciences

Standard Oil Co. Inc. was founded by John Rockefeller in 1870, who later established the Rockefeller Foundation (RF) in 1913. The oil industry might well have felt threatened by the discovery of atomic energy. The Republican Party had forged a close relationship with the oil industry, but the Democratic Party, led by F.D. Roosevelt (1933–1945) and H. Truman (1945–1953), governed the USA during and after WWII. When Republicans were reelected, Nelson Rockefeller was appointed as an important aide to President Eisenhower. Muller, in turn, had close ties to the RF. In 1954, the RF chose to finance a large project to evaluate ionizing radiation. RF asked the U.S. National Academy of Sciences (NAS) to organize the program, which was conducted under the auspices of NAS President Bronk of Rockefeller University, also an RF trustee. The Genetics Panel (GP) of the NAS Biological Effects of Atomic Radiation (BEAR) committee was established in 1954 and was chaired by Weaver, a mathematician and director of RF.

With no significant discussion, GP recommended LNT on June 12, 1956 [19]. The limit dose for nuclear workers of 500 mGy/y, which had been in place since 1934, was discarded. The next day, the front page of the New York Times, owned by an RF trustee, reported that radiation is dangerous. Other media followed suit. Soon, several leading biologists asked GP to provide documentation that supported LNT. GP refused to do so because they never possessed relevant data. This decision was cast, and reasonably so, as an ideologically motivated choice based on deliberate falsification and fabrication of research records [20]. Fossil fuel companies are opposed to nuclear energy even today.

### Expansion of LNT from insect sperm to the human body

Lewis (a 1995 Nobel laureate) argued in 1957 that radiation-induced leukemia conformed to the LNT hypothesis [21]. This was a new deployment of LNT from germ cells (heritable effects) to somatic cells (cancer induction). Several prominent researchers criticized the Lewis' paper (Table 2 in ref. [22]). With no convincing data to support LNT reported for half a century, the Biological Effects of Ionizing Radiation committee of NAS published BEIR VII report in 2006 to support LNT [23]. This report includes several shortcomings, as discussed later. Moreover, LNT has been applied also to chemical carcinogens; the smallest amount of a carcinogen is hazardous without threshold for positive excess risk.

## Radiation doses are underestimated by neglecting residual radiation or black rain

### Residual radiation and the formation of black rain

The radiation doses for A-bomb survivors were estimated using radiation transport calculations based on radiation transport findings from tests conducted on the ground in the Nevada desert. The nuclear weapons dropped on Hiroshima and Nagasaki were detonated respectively at 600 m and 503 m heights. To obtain more accurate data, the ICHIBAN project was planned, for which a 510 m high tower was constructed in the Nevada desert [24]. A nuclear reactor or other radiation source was placed at the top of the tower and data were collected. The dosimetry of the ICHIBAN project was named tentative dose 1965 (T65D). Around the 1980s, results demonstrated that T65D did not correctly reflect A-bomb radiation intensity. Exposure doses were reexamined, after which the Dose System 1986 (DS86) was established. In the period around the 1990s, DS86 was revised again; Dose System 2002 (DS02) was established. DS02 was revised further as DS02R1, producing the current system used to estimate the exposure doses of A-bomb survivors [25]. Although dose systems have been revised several times, T65D is the basic one. Others are modified versions that do not deviate greatly from T65D. T65D was an outcome of a large-scale simulation model of A-bombs, but it included an important oversight, i.e., omission of residual radiation with a dose twice as large as the initial radiation on which the dose estimation was made.

The energy of a typical A-bomb comprises three components: 35% thermal radiation (heat and light), 50%

blast energy (pressure shock wave), and 15% nuclear radiation [6]. Of that latter 15%, 5% is initial radiation (released within 30 s). The remaining 10% is residual radiation, which consists of major fallout and minor induced radioactivity. Induced radioactivity is produced by the action of neutrons in making non-radioactive substances into radioactive ones, but its lifespan is very short and is mostly negligible. A large fraction of the fallout, 40–70%, is believed to settle onto the ground within a day, but this depends strongly on weather and geographical features. When T65D was established, Black rain never fell in the Nevada desert. At Hiroshima and Nagasaki, thermal radiation incinerated or scalded plants, animals (including humans), houses, and various organic substances, producing heat, carbon dioxide, and vapor and consuming oxygen. Heat killed people. A lack of oxygen contributed deaths by suffocation. Victims were therefore affected in various ways by the A-bombs. From many waterways in Hiroshima and Nagasaki, large volumes of water were evaporated. The water itself was sucked up as if by a tornado. The vapor and water went up into the sky and cooled, thereafter forming raindrops containing soot and other debris. The resultant black rain started to pour down 20–30 min after the detonation. The rainfall lasted for a few hours (Fig. 2). The heavy black rain is well known to be highly radioactive. The possibility exists that the black rain included the most fallout, two-thirds of the nuclear radiation energy, i.e., twice as much radiation as the initial radiation used to estimate the radiation doses.

### Evidence that residual radiation fell to the ground with the black rain

An old Japanese article written in 1957 by G. Obo [26] was later translated into English [27]. For the article, approximately 4000 people who lived in a 7 km radius from the epicenter were interviewed personally if they entered the central area 1 km radius from the epicenter and if they had radiation acute effects such as skin burn, external injury, fever, diarrhea, sore throat, skin bleeding, or loss of hair. Students of Hiroshima University took part in this study. Fundamentally important data are presented in Fig. 3.

The left panel of Fig. 3 shows 1) positive relations between people with symptoms and distance from the epicenter, 2) outdoor people as more severely affected than indoor people as a matter of course, 3) people in the areas ≥3 km from ground zero (beyond the reach of γ-rays and neutrons from initial radiation) were affected, implying that this area was contaminated severely by residual radiation most probably carried by black rain, and 4) indoor and outdoor people who were at a distance ≥4 km and who entered the central areas were affected almost equally independent of their distance from the epicenter, strongly suggesting effects of residual radiation. The right panel of Fig. 3 shows that a large

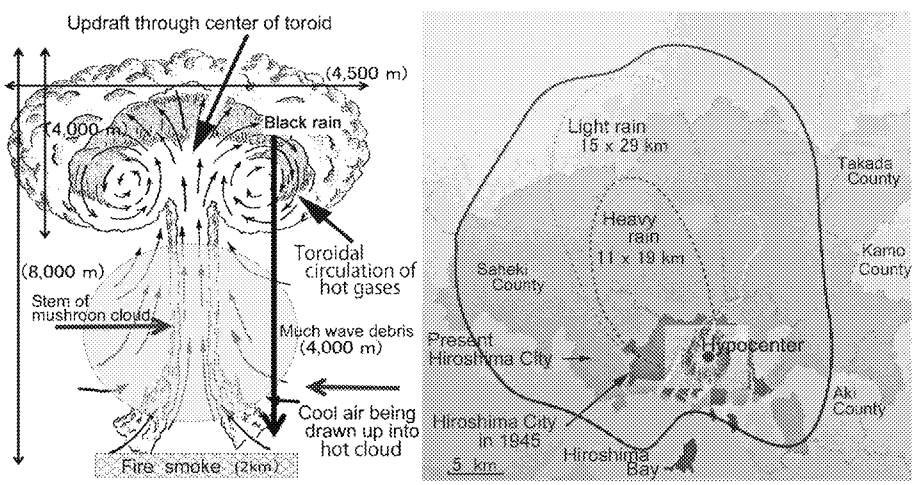



**Fig. 2** Formation of black rain from the mushroom cloud (left), and black rain areas (right) [27]. Left: The A-bombs used to attack Hiroshima (16 kt TNT equivalent) and Nagasaki (21 kt TNT equivalent) were detonated respectively at 600 m and 503 m heights. A 500-m diameter fireball is formed by the detonation of a 20 kt bomb. The fireball rose like a skyrocket. During expansion of the ball, vaporized matter was condensed to a doughnut-shaped cloud with violent internal circulatory motion. Following the rising fireball, dirt and debris were sucked up from the Earth's surface. A Mach wave (the tip reaching 560 m 1.25 s after the blast) was reflected from the surface, whirling soil and debris up to form a Mach wave mass of 3800 t, producing black rain with raw materials together with the mushroom components. Trees, lumber, and other matter of $1.55 \times 10^5$ t were incinerated, forming a smoky fire 2 km in diameter, above the ground. Two references [65, 66] were used to draw this figure. Right: The probable heavy rain area reported in 1953 is shown as a thick broken line. That of light rain is shown as a thin broken line. The black rain area according to analyses of the "A-bomb Survivors' health awareness survey" in 2008 is shown as a solid red line (Hiroshima Peace Memorial Museum). A red circle off center denotes the epicenter. Black dots around the epicenter show locations of A-bomb survivors at the T65D survey [67]

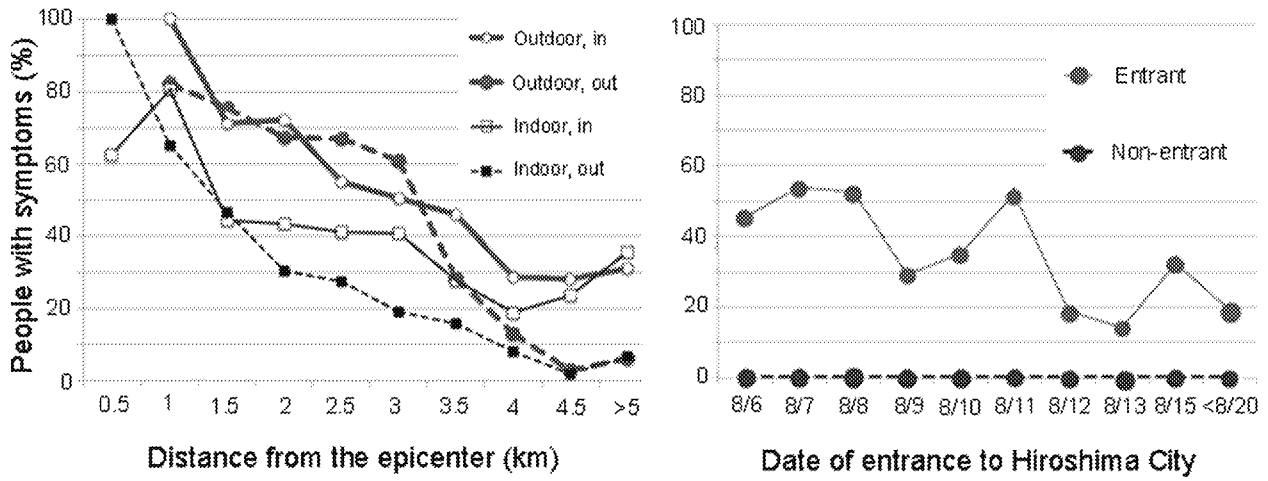



**Fig. 3** Proportion of A-bomb survivors with symptoms (left) and that of non-A-bomb survivors with symptoms (right) [27]: Left, open circles (Outdoor, in), outdoor A-bomb survivors who entered the central area; filled circles (Outdoor, out), outdoor survivors who did not enter the central area; open squares (indoor, in), indoor survivors who entered the central area; and filled square (indoor, out): indoor survivors who did not enter the central area. Right, red circles (entrant), non-A-bomb survivors who entered the central area and blue circle (non-entrant), non-A-bomb survivors who did not enter the central area

fraction of non-A-bomb survivors entered the central area 2–3 weeks after detonation suffered from severe radiation sickness as if they were A-bomb survivors. This result indicates strongly that the area was heavily contaminated with residual radiation associated with black rain.

### Report that black rain is negligible is refutable

The effects of black rain were studied using mortality data from 1950 to 2005 and cancer incidence data from 1958 to 2005 in Hiroshima and Nagasaki. The authors conclude that deleterious health effects from black rain exposure were not detected [28]. However, there is apparently a methodical fault. The authors asked people, "Was the person caught in Fallout Rain?" (Yes or No). According to the response, they were then divided into Yes or No groups. This grouping is almost meaningless because the important matter is not Yes or No, but if they had entered black rain affected areas within 2–3 weeks after detonation when residual materials remained active (Fig. 3). When solid cancer deaths and solid cancer incidence are extracted from the literature [29], excess relative risks (ERR) were smaller in the Yes group (caught in the rain) than in the No group (not caught in the rain) (Table 1). The data are suggestive of hormesis: slight radiation exposure is cancer-inhibitory.

The black rain affected areas were so wide that almost all A-bomb survivors and NIC must have been irradiated

**Table 1** Excess relative risks for exposure to black rain for solid cancer death and solid cancer incidence (solid cancer incidence for 1950–2005 and solid cancer death for 1958–2005 were not available)

| Data | Fallout rain status | No. of cases | Excess relative risk (ERR) |
|---|---|---|---|
| 1962–2005 | | | |
| Solid cancer death | No | 3573 | 0.00 |
| | Yes | 1483 | −0.04 |
| Solid cancer incidence No | 5653 | 0.00 | |
| | Yes | 2283 | −0.06 |
| 1950–2005 | | | |
| Solid cancer death | No | 3970 | 0.00 |
| | Yes | 1633 | −0.02 |
| 1958–2005 | | | |
| Solid cancer incidence | No | 5982 | 0.00 |
| | Yes | 2430 | −0.03 |

to a greater or lesser degree by residual radiation. The UNSCEAR 1958 report describes that almost all leukemia patients in zone C (1500–1999 m from ground zero) complained of severe radiation sickness in spite of an estimated dose of 50 rem (500 mSv in the International System of Units (SI)). Their doses must have been greater than 50 rem [30]. Exposure of around 2 Gy (close to 2 Sv in SI) is necessary to induce severe radiation sickness.

## BEIR VII report fails to support LNT

### BEIR VII report, the second problematic assertion by the National Academy of Sciences

Originally, LNT was based on Muller's experiments using repair-deficient *Drosophila* sperm [14]. He knew of the existence of thresholds for positive excess risk in *Drosophila* tests [17]. Indeed, later experiments by Japanese researchers indicate clearly that *Drosophila* irradiated with X-rays [31] or γ-rays [32] show not only thresholds but also hormesis. Hormesis has been observed in A-bomb survivors for solid cancers [29] and leukemia [33]. In spite of a large body of experimental data against LNT, NAS, the founder and advocator of LNT since 1956 [19], presented the BEIR VII report as basic LNT-supportive data (Fig. 4) [23]. The support, based on a Life Span Study (LSS) of A-bomb survivors, has been regarded as the gold standard to estimate radiation risk for human cancer. Nevertheless, this analysis presents serious flaws as explained below.

By the way, both Sv and Gy units are used according to original references in Fig. 4. Sv is a suitable unit for LNT and more generally acceptable Gy is used in this chapter.

### Leukemia, a better indicator of radiation stochastic effects than solid cancer

Leukemia, a cancer of the blood cells, is a better indicator of radiation than problematic solid cancers because it is sensitive to radiation. It appears around 2 years after exposure and reaches a peak 6–8 years later, whereas solid cancers start to appear around 10 years after exposure and last for decades. Figure 4 (upper left insert, blue arrow) shows that ERR/Gy for leukemia is approximately 2, whereas that for solid cancer is approximately 0.55 (lower left, purple arrow). Therefore, leukemia is sensitive to radiation and a better indicator than solid cancers. The dose-response of leukemia is not linear but is instead linear-quadratic (upper left insert). That of solid cancer also fits better to linear-quadratic (red arrow) than linearity (orange arrow), but no statistical significance was found between the two; BEIR VII asserts linearity. This forcible logic is difficult to accept. Moreover, when taking into consideration neglected residual radiation, effects of blast/thermal wave injury on the immune system, and hormesis, dose responses might be deviated far from linearity.

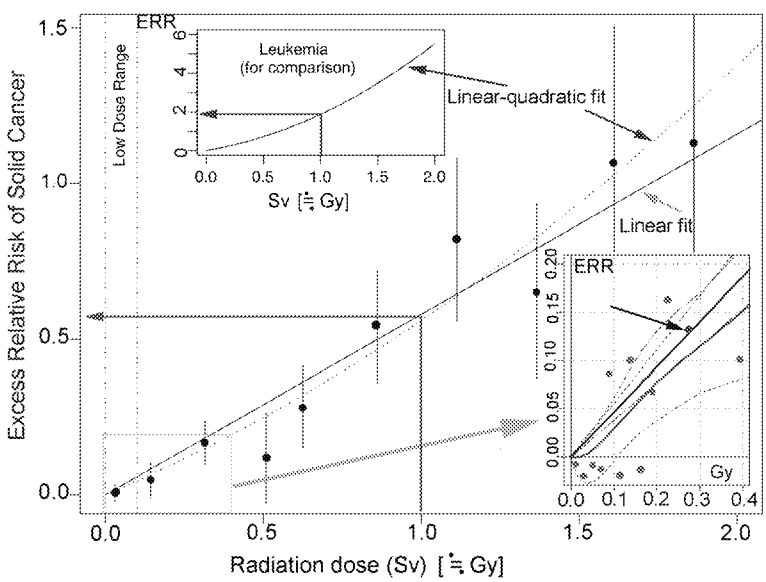



**Fig. 4** Excess relative risk (ERR) of solid cancers for Japanese A-bomb survivors [23]. The plotted vertical lines represent approximate 95% confidence intervals. The thin blue, purple, red, and orange arrows respectively indicate ERR/Sv for leukemia, ERR/Sv for solid cancer, linear quadratic fit, and linear fit. The lower left area in pale green is enlarged as the lower right insert, which shows the results of two statistical analyses [35]. The black straight and dotted lines respectively show the linear fit of LNT and 95% confidence intervals. The red continuous and dotted lines respectively show the Bayesian fit and 95% credible interval. The black arrow indicates only one dot inside the 95% confidence intervals. Less than 100 mSv constitutes the low-dose range

### Concealment of downturn

When radiation doses are much higher than 2 Gy, exposed people tend to die of adverse effects before reaching an age when cancer commonly occurs; ERR would show a downturn until finally reaching zero. The highest dose in Fig. 4 is 2 Gy, which conceals the downturn. Indeed, "The dose-response curve shows some downward bending in the high-dose range (2 + Gy in organ dose) for leukemia and even for all cancer except leukemia" [34]. When following the dots in Fig. 4 from low to high with downturn over 2 Gy in mind, one can easily imagine a sigmoid-like curve. This is shown by Bayesian analysis of LSS (Fig. 4, right below insert) [35]. A J-shaped curve is observed for solid cancers [36, 37] and leukemia mortality [33] in LSS. When hormesis and a downturn occur, the actual curve becomes instead an S-shaped curve [1].

### Averaging of low-dose groups

Doses < 100 mGy are the most important for our risk analyses. No significant differences were found between the control subjects and A-bomb survivors at these doses. The BEIR VII report combined all data points < 100 mGy, to which more than 80% of all survivors belong, together into one point (Fig. 4). This has been explained as an old statistical trick. It was used by Lewis to insist on the validity of LNT [21]. This dishonest representation was successful in giving the impression that the dose response is linear and that no thresholds exist. The low-dose area < 400 mGy (Fig. 4, lower left in pale green) is presented in detail (lower right in pale green) [35]. The ERR dots are dispersed widely: only 1 dot (black arrow in lower right insert) out of 12 is inside the 95% confidence interval, indicating that dose responses are not linear in this area.

### Inappropriate use of a false assumption (zero exposure-zero risk)

The line of LNT starts from zero according to the assumption that the exposure dose was zero and that ERR was zero in the control cohort (Fig. 4). This default model has been used to analyze LSS, but it is misleading because most A-bomb survivors and the control cohort people must have been exposed to residual radiation, as discussed later. The BEIR VII report based on that false assumption is therefore invalid. The dose-response line should not start from zero. Bayesian analysis does not assume this false assumption and allows more appropriate estimates. When the lower right insert of Fig. 4 is enlarged, crossing between the x-axis and the red line is roughly 25 mGy. An estimated zero dose might actually be 25 mGy. If these people were exposed to residual radiation, which was twice as great as the initial radiation, then A-bomb survivors and control subjects might have been exposed to additional 50 mGy: a total of 75 mGy.

### LNT ignores hormesis and thresholds

Granted that A-bomb survivors and control NIC people were exposed to 25–75 mGy over the estimates, the false assumption (zero exposure-zero risk) must be abandoned. Bayesian analysis, which does not need this assumption, allows negative responses, i.e., cancer mortality is suppressed to below the background level. Figure 4 shows that six responses are indeed hormetic (red dots under the x-axis in lower right insert). Therefore, low-dose radiation can suppress cancer deaths. At the same time, hormesis indicates that thresholds for positive excess risk can be established between hormetic and carcinogenic doses.

### Cherry picking of reference data

Siegel et al. [38] criticized The BEIR VII report in detail. One point is especially worthy of mention. The BEIR VII report cited that chromosomal aberrations induced by low-dose radiation in non-proliferating human cells were not repaired, thereby supporting LNT. However, that finding was a misrepresentation by failing to present that the aberrations in proliferating cells were repaired in several hours to the background level or less. Consequently, the result was opposite to what the BEIR VII argues.

## Low-dose radiation elongates A-bomb survivors' lifespan

### Earlier studies of lifespan elongation

Stewart and Kneale [39] showed that deaths in 1950–1982 from all non-malignant diseases in LSS population were significantly lower in survivors exposed to low doses than in unexposed persons. This U-shaped dose response relationship was refuted in comments by an LSS report [40], in which the mortality of A-bomb survivors was found to fit to the linear-threshold model (the estimated threshold is 1.4 Gy (DS86)) on the basis of LNT. Mine et al. [41] and Kondo [42] analyzed total deaths among about 100,000 A-bomb survivors in Nagasaki in1970–1988 and found that 290 males exposed to 0.5–1.49 Gy (T65D) showed significantly lower mortality. Although this beneficial effect was not found in female subjects, earlier studies [39, 41, 42] hint that A-bomb survivors exposed to low to intermediate doses live longer.

### Contradiction 1: Excess relative mortality of early entrants is lower than that of late entrants

A-bomb survivors' lifespans were apparently shortened as discussed earlier. Cologne and Preston's analyses [14] were based on LNT using an assumption of zero exposure and zero risk, with no consideration of the

possibility that lifespans could be elongated and that cancer deaths might be reduced. Their results are reproduced in Fig. 5.

As depicted in Fig. 3, early entrants were exposed to higher doses of residual radiation than late entrants. Excess relative mortality of early entrants, however, is lower than that of late entrants (Fig. 5A and B). The key to resolve this contradiction can be explained by radiation hormesis-related mechanisms (e.g., enhanced DNA damage repair, apoptotic removal of aberrant cells, and anticancer immunity stimulation): the B group people were exposed to higher residual radiation than the A group people. Exposure doses of the B group must be in a hormetic dose range.

### Contradiction 2: Excess relative mortality is inversely proportional to distance from the epicenter

Radiation doses are expected to be higher in proximal areas than in distal ones. If LNT is correct, then excess relative mortality must be higher in proximal areas. Data show inverse proportionality (Figs. 5C–F). Because the number of people is not small and mortality (death or life) data are accurate, the neat inverse proportionality must be close to the truth. Here again, this contradiction must be explained by radiation hormesis. People nearer the epicenter received more radiation than people farther away. Hormesis-related natural defense mechanisms also likely played a positive role in elongating the lifespan of survivors.

### Excess relative mortality shows a typical J-shaped curve, indicating hormesis and a threshold

The radiation dose group of 0.005–250 mGy (Fig. 4, G group) comprises 40,403 people. Its excess relative mortality is almost equal to that of all in-city individuals ($n = 34{,}064$, a total of C to F groups) whose radiation doses are estimated to be zero or < 0.005 mGy (Fig. 4, control level Y). Considering the large population size, a lack of health hazard observed in group G would not be ascribable to a simple fluctuation: it must reflect actual effects of 0–250 mGy. If they were exposed to residual radiation, which was twice as strong as the initial radiation, then they might have been exposed to additional 0–500 mGy, a total of 0–750 mGy.

The excess relative [43] mortality of H group (250–499 mGy is slightly higher than that of G group (0–250 mGy) and almost equal to D group (3–7 km from the epicenter). The mortality is below the control level X. These fluctuations are not random. At a glance from C to M in Fig. 5, one can see a beautiful J-shaped curve, an indicator of hormesis. When a J-shaped curve appears, we can establish a threshold at the crossing of the J and the x-axis. The threshold seems be between 250 and 499 mGy. Perhaps we could add 500–998 mGy of

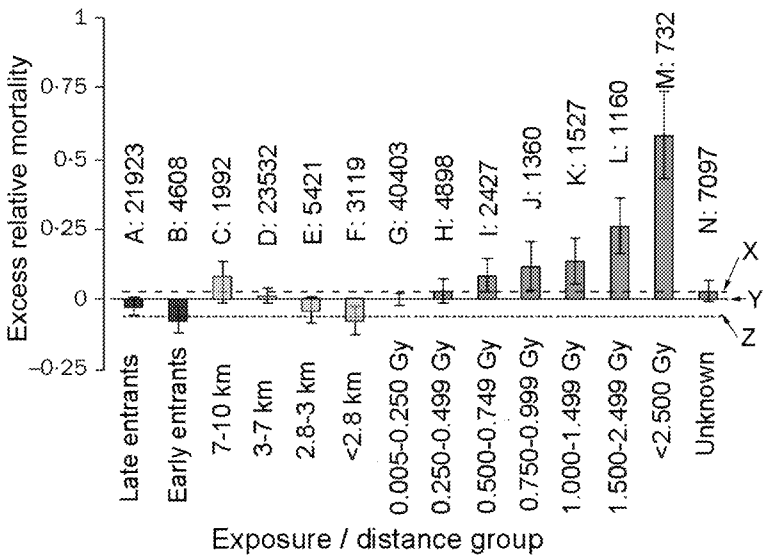



**Fig. 5** Excess relative mortality by radiation dose or distance from the hypocenter. Figure 1 and Table 1 of an earlier report [13] are combined. The scale from left to right shows increasing proximity to the epicenter: A, late entrants (not in city, entered after 1 month); B, early entrants (not in city, entered within 1 month); C–F, in city at time of A-bomb, with different distance from the epicenter; G–M, seven dose groups with different doses; and N, distance from the hypocenter = 0.11–3 km with unknown doses. Numerals above A–N denote the number of people examined. The comparison group Y (baseline mortality, or excess relative mortality 0) is all in-city individuals ($n = 34{,}064$) with estimated doses of zero or < 0.005 Gy. Dashed line X is the in city zero dose distal groups C and D ($n = 25{,}524$). Dotted line Z is the in-city zero-dose proximal groups E and F ($n = 8540$). Y is the combined data of X and Z

residual radiation, twice as much radiation as estimated doses.

## Cancer mortality of A-bomb survivors has been lower than the Japanese average

The US National Academy of Sciences proposed the spurious LNT in 1956 and put forward the problematic BEIR VII report in 2006 to support LNT (Fig. 4) [23]. The main reasons for the failure of the report are the use of LNT, use of the false assumption (zero exposure-zero risk), and neglect of hormesis effects. The Radiation Effects Research Foundation (RERF), a Japan–US scientific organization, has studied the health effects of A-bomb radiation. RERF has periodically reported research results and has insisted that the effects of radiation follow LNT in line with the BEIR VII report. The numbers of A-bomb survivors and solid cancer deaths are extracted from the latest three issues and are compared with Japanese averages (Table 2). The ratios of cancer deaths in both A-bomb survivors and NIC are smaller than those of Japanese averages. The numbers of people involved in Table 2 are not small. The differences are clear. Data must closely approximate reality. The finding that radiation of A-bombs reduces cancer mortality on average might be unexpected and incredible for LNT supporters. Nevertheless, such conclusions might be readily acceptable when one admits that low-dose radiation is hormetic under appropriate conditions and both A-bomb survivors and NIC who were exposed to low-dose radiation occupy a large fraction of the cohort. Consequently, low-dose radiation reduces cancer mortality on average and extends the lifespan (Fig. 5) as well.

## Discussion

### Earth has been exposed to ionizing radiation for billions of years

The current total heat flux from the Earth to space consists of half residual primordial heat and half radiogenic decay of uranium-238, and thorium-232, and potassium-40, the respective half lives of which are 4.46, 14.0, and 1.28 billion years [38]. Therefore, radioactivity was much higher 4 billion years ago when life started to appear on the earth. Radioactivity at our university campus in the air is less than 100 cpm, as measured with a Geiger–Muller counter, but that of nearby granite is around 500 cpm or so. Radioactive substances from the birth of the earth are still abundant on the earth now. Radon-222, a daughter of uranium-238, and radon-rich hot springs are frequently found around uranium ore.

### The human body receive roughly 20,000 radiation hits each second

In addition, carbon-14 and tritium-3 are constantly produced by the action of cosmic rays in the atmosphere. They are incorporated into our bodies. Japanese foods contain polonium-210 and potassium-40 and commit an effective dose of 0.47 mSv [44]. Consequently, the total of our annual background exposure dose is 2.1 mSv: cosmic rays (0.3 mSv), ground radiation (0.33 mSv), foods (0.99 mSv from carbon-14, polonium-210, and potassium-40), and aerial radon (0.48 mSv) [45]. When these radiation levels are converted to Bq (disintegration/second) using an Sv-Bq conversion table, rough estimation is 20,000 Bq. Potassium, an indispensable nutrient, and its associated potassium-40 (0.0117% of all naturally occurring potassium) contribute 4000 Bq. Therefore, we are exposed to by and large 20,000 radiation hits a second from not only the environment but also from materials inside our body. We ourselves are radioactive entities. In actuality, sleeping next to someone exposes one to 0.00005 mSv, which is the equivalent of eating half of a banana (0.0001 mSv). Living within 80 km of a nuclear plant and a coal plant for a year are, respectively, 0.00009 mSv and 0.0003 mSv. The dose of a chest X-ray is 0.02 mSv (ca. 1,000,000,000,000 hits [46]). A jet-liner flight from New York to London is 0.04 mSv [47]. Of course, these estimates are quite rough with significant uncertainties.

### Breathing is much more hazardous than low-dose radiation

The earth was anaerobic until 2.5 billion years ago when cyanobacteria started to add oxygen into the air. Oxygen

**Table 2** Comparison of solid cancer mortality in the lifespan study of A-bomb survivors with Japanese cancer mortality. Japanese average cancer deaths were calculated by dividing cancer deaths by total deaths each year during 1958–2009 [68]. Averages corresponding to survey periods were determined

| Reporters | Year | Survey period | No. *hibakusha* or [NIC[a]] | No. cancer deaths (%) | % Japanese average cancer deaths |
|---|---|---|---|---|---|
| Preston et al. [48] | 2007 | 1958–1998 105,427 | 17,448 (16.6) | 21.4 (1958–1998) | 21.4 (1958–1998) |
| | | | [25,4273,994 | (15.7)] | |
| Ozasa et al. [69] | 2012 | 1958–200 | 86,611 | 10,929 (12.6) | 22.3 (1958–2003) |
| | | | [26,529 | NA[b]] | |
| Grant et al. [70] | 2017 | 1958–2009 | 80,205 | 17,316 (21.5) | 23.3 (1958–2009) |
| | | | [25,239 | 5222 (20.6)] | |

[a], not in the city; [b], not available

is actually toxic, but it is useful to produce energy effectively through oxidative phosphorylation. Our ancestors started to use oxygen, but reactive oxygen species (ROS) are inescapable byproducts of the oxidative process. ROS themselves are toxic. Nine billion ROS are produced in a cell a day [48]. We developed systems to quench ROS instantaneously using radical scavengers such as glutathione and L-cysteine and using enzymes such as superoxide dismutase and catalase.

Hazards by both respiration and low-dose ionizing radiation are caused mainly by ROS, but ROS production by respiration overwhelms that by low-dose radiation by thousands to a million of times the magnitude. ROS-quenching systems developed under intensive ionizing radiation conditions for more than billion years before the appearance of oxygen in the air must be readily applied to quench ROS by respiration.

### Low-dose radiation is not only beneficial but necessary

A benefit of oxygen beyond energy production is the shielding of ultraviolet (UV) light. We sometimes expose clothes and mats to the sunlight to dry them and simultaneously kill bacteria, fungi, and ticks. We are suntanned in the sun, by which dead epithelial cells are shed from the skin when UV is strong. When oxygen was not in the air, UV was so strong that organisms were unable to live on the ground. The ozone layer cuts most UV; organisms today can move across the ground. Although UV can kill some organisms, it is indispensable to produce vitamin D. We are using the toxic UV as a need. So are ROS. When leukocytes "eat" bacteria, they enzymatically produce large quantities of ROS to kill them. ROS are sufficient to kill bacteria, but cells are also killed later. We used to see pus, a pile of dead leukocytes, in or around the wound before antibiotics became popular. In fact, J.F. Miesher extracted DNA from pus for the first time in 1869.

Figure 5 and Table 2 respectively show radiation-hormesis-related benefits: 1) elongating of lifespan and 2) reduced cancer deaths. Other analyses of LSS show hormesis in solid cancers [29] and leukemia [33]. Hormesis has been reported for many organisms such as protozoa [38], Drosophila [31, 32], and mice [49]. Lung cancer incidence of humans exposed to radon-222 is also hormetic [50]. These are some examples, constituting only the tip of the iceberg. Radiation-hormesis-related health benefits are possibly universal among all living organisms. Low-dose radiation is apparently not only beneficial but also necessary. When human cells were cultured under unshielded (1.75 mGy/y) and 10 cm lead-shielded (0.3 mGy/y) conditions, heat shock proteins (products of adaptive responses) were produced more in shielded cells than in unshielded cells, indicating that reduced radiation was not relief, but was stressful to the cells [51]. When bacteria were cultured 650 m underground, where radiation levels were 1/80 those at ground level, bacterial growth was retarded [51, 52]. If LNT is correct, then growth should be enhanced by removal of hazardous ionizing radiation. The results were the opposite, indicating the failure of LNT. Low-dose radiation is sensed by bacteria and gene expression is changed greatly at the transcriptional level [48].

### Systematically associated many-layered defense mechanisms that LNT ignores

The sanctuary zone of a 30 km radius in Chernobyl is a paradise for animals and birds. More than 315 species thrive there. Glutathione levels of rats are elevated, but no DNA lesions are found on the animals. Levels of this radical scavenger in birds of 16 species are also high [53]. The authors argue that hormesis is working there. Consequently, ROS are quenched before attacking DNA. If DNA is injured by a large amount of ROS, cells can repair most of them. If DNA injuries exceed the repair capacity, cells are killed by apoptosis and are removed. If cancerous cells are produced, then most of them are removed by vigilant survey of immune systems. These adaptive defense systems are only some examples acquired by living organisms through evolution as innate essential attributes. Humans have the ability to sense crisis and to prepare for defense. Even if ionizing radiation is neither seen nor sensed, its products, ROS, constitute signaling molecules for defense systems. Defense systems at various levels (cells, tissues, organs, etc.) by various mechanisms (ROS quenching, DNA repair, apoptosis, anticancer immunity, etc.) must be associated with hormetic dose-response relationship for radiation induced cancer. A fundamental failure of LNT is that it ignores these time-requiring biological systems. Indeed, LNT is aptly accused of "epidemiology without biology" [54].

### Magic of epidemiology to change negative to positive

A large body of experimentally obtained results collectively indicates radiation hormesis, but LNT proponents ignore these data. Risk of death from leukemia and lymphoma in more than 300,000 radiation-monitored workers (INWORKS) was studied. Results indicate that the dose-response matched well with LNT [55]. This result was praised in an internationally prestigious journal: *Nature* [56]. Soon more than 20 researchers raised objections, some of which included 1) lack of negative control, 2) LNT-based analyses, 3) no consideration of natural background and smoking, 4) 90% confidence limits (usually 95%) to achieve easy statistical significance, 5) one-tailed tests ignoring possible hormetic response, and 6) primitive miscalculations a schoolboy would not make. Soon a correction appeared in *Nature*, "The original version of this article incorrectly calculated

an 'expected' death rate from leukaemia among the workers, and as a result, the risk posed by radiation increments was wrong. The story has been corrected to reflect this." At least two works have leveled detailed criticisms against INWORKS studies [57, 58]. Epidemiology is apparently the last foothold for LNT, but "flexibility in data collection and analysis allows presenting anything as significant" [59]. The present author required no sophisticated epidemiology to find the opposite of what the authors assert in elongation of lifespan in Fig. 5 and a decrease of cancer mortality in Table 2.

### Tremendous human, social, and economic losses caused by obstinate application of the linear no-threshold model

The individual external doses of 421,394 Fukushima residents for the first 4 months after the 2011 earthquake and tsunami were the following: 62.0%, < 1 mSv; 94.0%, < 2 mSv; 99.4%, < 3 mSv. The arithmetic mean and maximum for individual external doses were 0.8 and 25 mSv, respectively [60]. When actual external exposure doses estimated by individual glass-badge measurements in Date City, Fukushima, were compared with official ambient doses presented by the Japanese government, the ratio was 0.15 [61]. If this figure is applied to the data above [51], then the effective doses can be calculated as follows: 62.0%, < 0.15 mSv; 94.0%, < 0.3 mSv; 99.4%, < 0.45 mSv. The respective mean and maximum doses were 0.12 and 3.75 mSv. Even the maximum external dose is below the Japanese average medical exposure dose: 4 mSv. At the time of the Fukxushima nuclear accident, the International Commission on Radiological Protection (ICRP) recommended reference levels of 20–100 mSv [62]. Less than 100 mSv, the so-called low-dose range (Fig. 4), is accepted as representing no difference between exposed and non-exposed people. These are acute doses. Hazardous effects can be reduced to 1/16.5 by prolonged radiation such as in Fukushima [63], meaning that 1.65 Sv (100 × 16.4 mSv) might be non-hazardous. If it were not for LNT, evacuation would not have been necessary in Chernobyl or Fukushima [37]. In Ramsar, Iran, people have lived continuously in environments of 260 mSv with no health problems [56]. Tremendous human, social, and economic losses caused by obstinate application of the failed LNT could have been avoided [3]. In truth, LNT is a deeply immoral. Prof. G. Walinder's words, "The LNT hypothesis is a primitive, unscientific idea that cannot be justified by current scientific understanding. As practiced by the modern radiation protection community, the LNT hypothesis is one of the greatest scientific scandals of our time." Madame M. Curie's words, "Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we might fear less." It is the time to reconsider the use of the LNT [64]. The author's sincere hope is that some unmasking of LNT can help Fukushima people and others to live their lives free of irrational fear.

## Conclusion

The linear no-threshold hypothesis (LNT) was recommended without solid data by the National Academy of Sciences in 1956. The academy put forward the BEIR VII report in 2006 as supporting evidence of LNT. This report was based on the Life Span Study (LSS) of A-bomb survivors. LSS has three major defects: 1) Residual radiation to which both A-bomb survivors and control subjects were exposed was neglected. Specifically, the control subjects were not valid as representing the negative control. 2) LNT is the basis of risk analyses. The failed model cannot be used. 3) Radiation hormesis is beyond the scope of LSS, but it actually occurs. The average lifespan of A-bomb survivors is longer than the Japanese average. Solid cancer deaths of A-bomb survivors and control subjects were fewer than the Japanese average. Consequently, one can reasonably infer that radiation of A-bombs elongated their lifespan and reduced cancer deaths on average, indicating a failure of LNT. Unfortunately, LNT has served as the basis of radiation regulation. If it were not for LNT, then evacuation of Fukushima people would not have been mandated and tremendous human, social, and economic losses would have been avoided. To avoid unnecessary losses and fear, humanity must learn as soon as possible that low-dose radiation is not only harmless but beneficial.

#### Abbreviations

BEAR: Biological Effects of Atomic Radiation; BEIR: Biological Effects of Ionizing Radiation; ERR: Excess relative risk; GP: Genetics Panel; ICRP: International Commission on Radiological Protection; LET: Linear energy transfer; LNT: linear no-threshold model; LSS: Life Span Study; NAS: National Academy of Sciences of the United States of America; NIC: not-in-the-city; RERF: Radiation Effects Research Foundation; RF: Rockefeller Foundation; SI: International System of Units; USA: United States of America

#### Acknowledgements

I am a member of Scientists for Accurate Radiation Information (SARI). Let me express my thanks to SARIans for their supply of valuable information. I am grateful to Prof. Edward J. Calabrese for providing me with excellent papers, only a few of which could be cited here. This paper is dedicated to the late Prof. Kimiyuki Tsuchiya who passed away on June 5, 2018. I met him at the National Institute of Genetics in 1972. He captured spiny county rats in Tokunoshima (*Tokudaia tokunoshimensis* Endo & Tsuchiya, for which karyotypes of both sexes are the same and the chromosome number is 45) and Amami Islands (*Tokudaia osimensis*, for which karyotype of both sexes are the same and the chromosome number is 25). Together, we showed that they have no mammalian sex determining gene *SRY*. Pancreatic cancer was found in Dr. Tsuchiya 1 year and 9 months ago. I recommended radiation hormesis therapy to him. He showed willingness to use it, but LNT has prevented development of this therapy in Japan.

#### Funding

This work was supported by Sutou Life Science Inc.

#### Availability of data and materials

All data generated or analyzed during this study are included in this published article.

### Author's contribution
The author read and approved the final manuscript.

### Author's information
The author was taught that ionizing radiation is limitlessly hazardous until March 2011. On the occasion of volunteer activity in Fukushima to measure contamination of evacuees, I examined the effects of ionizing radiation and found that LNT is invalid. As a scientist, I would like to relieve as many people as possible from unreasonable belief in LNT.

### Ethics approval and consent to participate
Not applicable.

### Consent for publication
Not applicable

### Competing interests
The author declares that he has no competing interest related to this report.

## Publisher's Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 16 August 2018 Accepted: 13 November 2018
Published online: 19 December 2018

### References
1. Sutou SA. message to Fukushima: don't fear radiation so much. Tokyo: Gentosha; 2017. (in Japanese)
2. Sutou S, Tanooka H, Doss M, editors. Fukushima nuclear accident: global implications, long- term health effects and ecological consequences. New York: Nova Sciences Publishers Inc.; 2015.
3. Sutou S. Tremendous human, social, and economic losses caused by obstinate application of the hailed linear no-threshold model. Yakugaku Zasshi. 2015;135:1197–211 (in Japanese). https://www.jstage.jst.go.jp/article/yakushi/135/11/135_15-00188/_pdf/-char/ja. Accessed 1 Oct 2018.
4. Sutou S. A message to Fukushima: nothing to fear but fear itself. Genes Environ. 2016;38:12 https://genesenvironment.biomedcentral.com/articles/10.1186/s41021-016-0039-7. Accessed 1 Oct 2018.
5. Calabrese EJ. From Muller to mechanism: how LNT became the default model for cancer risk assessment. Environ Pollut. 2018;241:289–302.
6. Glasstone S, Philip J. Editors. Effects of nuclear weapons, 3rd Ed. united State Department of Defence and the energy Research and Development Administration. Washington DC: U.S. Government Printing Office; 1977.
7. Ducoff H. Radiation hormesis: incredible or inevitable? Korean J Bio Sci. 2002;6:187–93.
8. Feinendegen LE. Evidence for beneficial low level radiation effects and radiation hormesis. Brit J Radiol. 2005;78:3–7.
9. Jaworowski Z. Radiation hormesis-a remedy for fear. Hum Exp Toxicol. 2010; 29:263–70.
10. Calabrese EJ, Stanek EJ 3rd, Nascarella MA. Evidence for hormesis in mutagenicity dose- response relationships. Mutat Res. 2011;726:91–7.
11. https://en.wikipedia.org/wiki/Tsutomu_Yamaguchi. Accessed 1 Oct 2018.
12. Wiles D. On radium and radiation. CNS Bull. 2014;35:10–1.
13. Calabrese EJ. Was Muller's 1946 Nobel prize research for radiation-induced gene mutations peer reviewed? Philos Ethics Humanit Med. 2018;13:2–5.
14. Cologne JB, Preston DL. Longevity of atomic-bomb survivors. Lancet. 2000; 356:303–7.
15. Caspari E, Stern C. The influence of chronic irradiation with gamma rays at low dosages on the mutation rate in *Drosophila melanogaster*. Genetics. 1948;33:75–95.
16. Muller HJ. https://www.nobelprize.org/nobel_prizes/medicine/laureates/1946/muller-lecture.html. Accessed 1 Oct 2018.
17. Anonymous. Genetic effects of atomic radiation. Science. 1956;123:1157–64.
18. Calabrese EJ. LNTgate: the ideological history of cancer risk assessment. Toxicol Res Appl. 2017:1–3 http://journals.sagepub.com/doi/pdf/10.1177/2397847317694998. Accessed 1 Oct 2018.
19. Lewis EB. Leukemia and ionizing radiation. Science. 1957;125:965–72.
20. Calabrese EJ. The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment. Arch Toxicol. 2009;83:203–25.
21. National Research Coucil of the National Academies. Health risks from exposure to low levels of ionizing radiation: BEIR VII – Phase 2. 2006. http://www.philrutherford.com/Radiation_Risk/BEIR/BEIR_VII.pdf. Accessed 1 Oct 2018.
22. Auxier JA. ICHIBAN: the dosimetry program for nuclear bomb survivors of Hiroshima and Nagasaki – a status report as of April 1 (1964). http://digicoll.manoa.hawaii.edu/techreports/PDF/CEX-64.3.pdf. Accessed 1 Oct 2018.
23. Funamoto S, Marumo K, Sakata R, Kodama Y, Ozasa K, Kodama K. DS02R1: improvements to atomic bomb Survivors' input data and implementation of dosimetry system 2002 (DS02) and resulting changes in estimated doses. Health Phys. 2017;112:56–97.
24. Obo G. Statistical observation of disorders induced by residual radiation of atomic bomb. Nihon Iji Shinpo. 1957;1746:21–5 (in Japanese).
25. Sutou S. Rediscovery of an old article that the area around the epicenter in Hiroshima was heavily contaminated with residual radiation, indicating that exposure doses of A-bomb survivors were largely underestimated. J Radiat Res. 2017;58:745–54 https://academic.oup.com/jrr/article/58/5/745/3926493. Accessed 1 Oct 2018.
26. Luckey TD. Biological effects of ionizing radiation: a perspective for Japan. J Am Phys Surg. 2011;16:45–6.
27. Sakata R, Grant EJ, Furukawa K, Misumi M, Cullings H, Ozasa K, et al. Long-term effects of the rain exposure shortly after the atomic bombings in Hiroshima and Nagasaki. Radiat Res. 2014;182:599–606.
28. Cuttler JM. Nuclear energy and the LNT hypothesis of radiation carcinogenesis. In: Sutou S, Tanooka H, Doss M, editors. Fukushima nuclear accident: global implications, long-term health effects and ecological consequences. New York: Nova Sciences Publishers Inc; 2015. p. 27–60.
29. Sakata R, Grant EJ, Furukawa K, Misumi M, Cullings H, Ozasa K et al. Long-term effects of the rain exposure shortly after the atomic bombings in Hiroshima and Nagasaki. Radiat Res.
30. Shimizu Y, Kato H, Schull WJ, Hoel DG. Studies of the mortality of A-bomb survivors. 9. Mortality, 1950-1985: part 2. Cancer mortality based on the recently revised doses (DS86). Radiat Res. 1990;121:120–41.
31. Furukawa KM, Cologne JB, Cullings HMA. Bayesian semiparametric model for radiation dose-response estimation. Risk Anal. 2016;36:1–13.
32. SMJ Mortazavi SMJ, Mohan DM. Comments on "Solid cancer incidence among the life span study of Atomic Bomb Survivors: 1958-2009"(Radiat Res, 2017;187:513-37). Radiat Res. 2017;188:369–71.
33. Siegel JA, Greenspan BS, Maurer AH, Taylor AT, Phillips WT, Nostand DV, et al. The BEIR VII estimates of low-dose radiation health risks are based on faulty assumptions and data analyses: a call for reassessment. J Nucl Med 2018. https://www.ncbi.nlm.nih.gov/pubmed/29475999. Accessed 1 Oct 2018.
34. Shimizu Y, Kato H, Schull WJ. Studies of the mortality of A-bomb survivors. 9. Mortality, 1950-1985: part 3. Noncancer mortality based on the revised doses (DS86). Radiat Res. 1992;130:249–66.
35. Stewart AM, Kneale GW. Late effects of A-bomb radiateon: risk problems un-related to the new dosimetery. Health Phys. 1988;54:567–9.
36. Mine M, Okumura Y, Ichimaru M, Nakamura T, Kondo S. Apparently beneficial effect of low to intermediate doses of A-bomb radiation on human lifespan. Int J Radiat Biol. 1990;58:1035–43.
37. Kondo S. Health effect of low-level radiation. Osaka: Kinki University Press; 1993.
38. The KamLAND Collaboration. Partial radiogenic heat model for earth revealed by geoneutrino measurements. Nat Geosci. 2011;4:647–51.
39. Sugiyama H, Terada H, Isomura K, Iijima I, Kobayashi J, Kitamura K, et al. Internal exposure to $^{210}$Po and $^{40}$K from ingestion of cooked daily foodstuffs for adults in Japan. J Toxicol Sci. 2009;34:417–25.
40. Environmental radioactivity (estimation of radiation dose in Japan) (new edition). Tokyo: Nuclear Safety Research Association;2011. (in Japanese).
41. Cohen B, Lehr J. Risk in perspective: Radiation, reactor accidents, and radioactive waste. https://www.radonmine.com/pdf/riskinperspective.pdf. Accessed 1 Oct 2018.
42. Radiation dose chart. https://xkcd.com/radiation/ Accessed 1 Oct 2018.
43. Ozasa K, Shimizu Y, Suyama A, Kasagi F, Soda M, Grant EJ, et al. Studies of the mortality of atomic bomb survivors, report 14, 1950-2003: an overview of cancer and non cancer diseases. Radiat Res. 2012;177:229–43.
44. Smith GB, Grof Y, Navarrette A, Guilmette RA. Exploring biological effects of low level radiation from the other side of background. Health Phys. 2011; 100:263–5.
45. Castillo H, Smith GB. Below-background ionizing radiation as an environmental cue for bacteria. Front Microbiol 8:177. https://doi.org/10.3389/fmicb.2017.00177. Accessed 1 Oct 2018.

46. Castillo H, Li X, Schilkey F, Smith GB. Transcriptome analysis reveals a stress response of *Shewanella oneidensis* deprived of background levels of ionizing radiation. PLoS One. 2018;13(5):e0196472 https://doi.org/10.1371/journal.pone.0196472. Accessed 1 Oct 2018.
47. Galvan I, Bonisoli-Alquati A, Jenkinson S, Ghanem G, Wakamatsu K, Mousseau TA, et al. Chronic exposure to low-dose radiation at Chernobyl favours adaptation to oxidative stress in birds. Funct Ecol. 2014;28:387–403.
48. Pollycove M, Feinendegen LE. Radiation induced versus endogenous DNA damage: possible effect of inducible protective responses in mitigating endogenous damage. Br J Radiol. 2005;78:3–7.
49. Abbott A. Researchers pin down risks of low-dose radiation. Nature. 2015; 523:17–8.
50. Scott BRA. Critique of recent epidemiologic studies of Cancer mortality among nuclear workers. Dose Response. 2018;16(2):1559325818778702 https://doi.org/10.1177/1559325818778702.
51. Doss M. INWORKS study does not provide evidence for increase in solid cancers from protracted exposure to low doses of ionizing radiation. Lancet Haematol. 2015;2(10):e404–5 https://doi.org/10.1016/S2352-3026(15)00145-3.
52. Simmons JP, Nelson LD, Simonsohn U. False positive psychology: undisclosed flexibility in data collection and analysis allows presenting anything as significant. Psychol Sci. 2011;22:1359–66.
53. Miyazaki M, Hayano R. Individual external dose monitoring of all citizens of date City by passive dosimeter 5 to 51 months after the Fukushima NPP accident (series): 1. Comparison of individual dose with ambient dose rate monitored by aircraft surveys. J Radiol Prot. 2016;37:1–12.
54. International Commission on Radiological Protection. Fukushima nuclear power plant accident. ICRP ref: 4847-5603-4313. Mar 21, 2011. http://www.icrp.org/docs/fukushima%20nuclear%20power%20plant%20accident.pdf. Accessed 1 Oct 2018.
55. Tanooka H. Dose rate problems in extrapolation of Hiroshima-Nagasaki atomic bomb data to estimation of cancer risk of elevated environmental radiation in Fukushima. In: Sutou S, Tanooka H, Doss M, editors. Fukushima nuclear accident: global implications, long-term health effects and ecological consequences. New York: Nova Sciences Publishers Inc; 2015. p. 101–13.
56. Mortazavi SMJ. High background radiation areas of Ramsar on the cover of Nuclear News of The American Nuclear Society (ANS) Published on November 16, 1-14, 2017. https://www.linkedin.com/pulse/high-background-radiation-areas-ramsar-cover-nuclear-news-mortazavi/?trackingId=FKAL851G9zCpxrZRiNeW8Q%253. Accessed 1 Oct 2018.
57. Cardarelli JJ II, Ulsh BA. It is time to move beyond the linear no-threshold theory for low-dose radiation protection. Dose-Response 2018;April-June:1-24. DOI:https://doi.org/10.1177/1559325818779651.
58. http://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000049131.html. Accessed 1 Oct 2018.
59. Vital Statistics Japan Ministry of Health, Labour, and Welfare (cancer_mortality(1958- 016).xls in https://ganjoho.jp/reg_stat/statistics/dl/index.html. Accessed 1 Oct 2018.
60. Glaser A. Effects of nuclear weapons: Princeton University; 2007. http://www.princeton.edu/~aglaser/lecture2007_weaponeffects.pdf. Accessed 1 Oct 2018
61. Maruyama T, Yoshikawa T. Residual radiation by black rain in Hiroshima A-bomb and radiation exposure doses. In: Hasai H, Hoshi H, Shibata S, et al., editors. Proceedings of the workshop 'new radiation dosimetry system DS02 of the atomic bombing in Hiroshima and Nagasaki'. Kyoto: Kyoto University; 2005. p. 184–97. (in Japanese).
62. Fujita S, Cullings H, Preston D, Funamoto S, Teranishi S, Grant E, et al. Exposure dose calculation of hibakusha by DS02 at the radiation effects Research Foundation. In: Hasai H, Hoshi H, Shibata S, et al., editors. Proceedings of the workshop 'new radiation dosimetry system DS02 of the atomic bombing in Hiroshima and Nagasaki'. Kyoto: Kyoto University; 2005. p. 142–9. (in Japanese).
63. Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, et al. Solid cancer incidence in atomic bomb survivors: 1958-1998. Radiat Res. 2007;168:1–64.
64. Grant EJ, Brenner A, Sugiyama H, Sakata R, Sadakane A, Utada M, et al. Solid Cancer incidence among the life span study of atomic bomb survivors: 1958-2009. Radiat Res. 2017;187:513–37.
65. UNSCEAR. Report of the United Nations Scientific Committee on the effects of atomic radiation, United Nations, General Assembly, Supplement No. 17. 1958. p. 165.
66. Koana T, Takashima Y, Okada MO, Ikehata M, Miyakoshi J, Sakai K. A threshold exists in the dose-response relationship for somatic mutation frequency indicated by x irradiation of *Drosophila*. Rad Res. 2004;161:391–6.
67. Ogura K, Magae J, Kawakami Y, Koana T. Reduction in mutation frequency by very low-dose gamma irradiation of *Drosophila melanogaster* germ cells. Radiat Res. 2009;171:1–8.
68. Muller HJ. Artificial transmutation of the gene. Science. 1927;66:84–7.
69. Luckey TD. Ionizing radiation promotes protozoan reproduction. Radiat Res. 1986;108:215–21.
70. Ina Y, Sakai K. Prolongation of life span associated with immunological modification by chronic low-dose-rate irradiation in MRL-lpr/lpr mice. Radiat Res. 2004;161:168–73.



**Ready to submit your research? Choose BMC and benefit from:**

- **fast, convenient online submission**
- **thorough peer review by experienced researchers in your field**
- **rapid publication on acceptance**
- **support for research data, including large and complex data types**
- **gold Open Access which fosters wider collaboration and increased citations**
- **maximum visibility for your research: over 100M website views per year**

**At BMC, research is always in progress.**

**Learn more** biomedcentral.com/submissions

BMC

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 5/29/2018 1:03:03 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Attachments**: Environ. Pollut. Muller-Mech-1.pdf

Clint:

Question: The LNT story (see attached) is truly an amazing one.....it simply shows the horrible Foundation that cancer risk assessment was/is based on and how society is victimized by Fraud at the highest levels. Is this something that the EPA would be interested in developing a documentary on? This is really one of the next important steps forward.

Ed

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 5/26/2018 9:10:14 AM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: new LNT paper
**Attachments**: Environ. Pollut. Muller-Mech-1.pdf

Clint:

See new LNT paper as of this morning!!

Ed

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 5/25/2019 2:32:43 AM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: new LNT paper
**Attachments**: CBI-Calabrese-LNT-2.pdf

Clint:

See my latest paper on LNT....published today.

Ed

Chemico-Biological Interactions 308 (2019) 110–112

Contents lists available at ScienceDirect

Chemico-Biological Interactions

journal homepage: www.elsevier.com/locate/chembioint

# EPA adopts LNT: New historical perspectives

Edward J. Calabrese

*Department of Environmental Health Sciences, Morrill I, N344, University of Massachusetts, Amherst, MA, 01003, USA*

ARTICLE INFO

*Keywords:*
LNT
Cancer risk assessment
Dose response
Threshold dose response
Somatic mutation
Environmental protection agency

ABSTRACT

This paper provides an historical assessment of how the linear non-threshold (LNT) model became adopted as policy by the United States Environmental Protection Agency (US EPA) in 1975 [1] and how prior United States National Academy of Sciences (US NAS) radiation advisory panels may have affected this EPA decision. The paper highlights a generally unrecognized set of recommendations of the 1960 Biological Effect of Atomic Radiation [2] Genetics and Medical/Pathology Panels that did not support LNT for cancer risk assessment due to their judgements of its scientific limitations and unacceptable uncertainties. These convergent, independent and high profile recommendations were not promoted by the sponsors (i.e., Rockefeller Foundation and the NAS), and were ignored by the media, Congress and the scientific community in contrast to the vast attention directed to the linearity recommendation for germ cell mutation by the BEAR Genetics Panel in 1956 [3,4]. The subsequent Biological Effects of Ionizing Radiation (BEIR) I Committee (1972) [5] report ignored these BEAR Panel (1960) [2] recommendations, only commenting on the BEAR 1956 linearity supporting recommendation [3,4]. These actions are documented and assessed for how they influenced why and how EPA adopted linearity for cancer risk assessment based on the BEIR I report.

## 1. Introduction

In 1956, the US National Academy of Sciences (NAS) Biological Effects of Atomic Radiation (BEAR) I Genetics Panel [3,4] recommended that risk assessment for ionizing radiation for germ cell mutation be switched from a threshold to a linear dose response. This was a precipitous moment in risk assessment history that was long anticipated and highly publicized (e.g. it became a prominent paper in the journal *Science*, front page stories in the *New York Times* and *Washington Post* and other major outlets with the report sent to all public libraries in the United States) [6]. The NAS BEAR I Genetics Panel was considered the 1950's equivalent of a genetics "Dream Team", having great influence and standing within the scientific, legislative, regulatory, news media and general public communities. Their report was followed by Congressional Hearings in 1957 [7,8] and influenced advisory groups such as the National Council on Radiation Protection and Measurements (NCRPM) to adopt a linear dose response for cancer risk assessment in December 1958 [9], which, itself, proved to be a similarly major development [8,10].

## 2. NCRPM cancer risk assessment linearity recommendation

The December 1958 NCRPM position [9] was based on the assumption that radiation induced genetic damage is "completely cumulative and that the effect is independent of the rate at which the radiation is delivered." [11]. This statement embraces the geneticist mantra of the 1950s and the position of the 1956 NAS BEAR Genetics Panel Report [3,4]. However, in contrast to the scientific beliefs of the 1956 BEAR Genetics Panel [3,4], the 1960 NCRPM [11] statement did not accept these assumptions and conclusions as established facts; the NCRPM specifically stated that they were adopted as prudent public health policy, reflecting in effect a Precautionary Principle. The timing of the 1958 NCRPM policy meeting (Dec. 29/30, 1958) [9] was remarkable being about two weeks after the seminal publication of Russell et al. in the journal *Science* on December 19th, 1958 [12] demonstrating that radiation-induced mutation frequency was explained by dose rate, not total dose, and that such mutations could be readily repaired. There has been no record yet obtained that clarifies why the decision to adopt a linear dose response policy by the NCRPM was not affected by the Russell et al. [12] findings since James Crow and Edwin B Lewis, both prominent figures in the radiation geneticist community, were members of the NCRPM Committee. That is, why didn't NCRPM delay this decision, pending a review of the Russell findings [12]?

Of particular relevance to the LNT issue is that the 1956 BEAR Medical/Pathology Panel [4,13], which met concurrently with the BEAR Genetics Panel, offered a different perspective/evaluation of ionizing radiation induced mutation and its relationship to cancer as did the Genetics Panel. The Medical/Pathology Panel downplayed and even

*E-mail address:* edwardc@schoolph.umass.edu.

https://doi.org/10.1016/j.cbi.2019.05.027
Received 25 April 2019; Received in revised form 13 May 2019; Accepted 15 May 2019
Available online 17 May 2019
0009-2797/ © 2019 Elsevier B.V. All rights reserved.

questioned the role of somatic mutation in cancer as seen in the following comment. "If somatic mutation is a necessary part of the induction of cancer, it would seem to play a minor role." (page 62, right column) [13]. They also noted that at the permissible dose level for germ cells as recommended for large populations by the Genetics Panel "there would be no demonstrable somatic effect .... " (page 62, right column) [13]. This conclusion was supportive of a threshold dose response for both somatic mutation and cancer. This perspective was not highlighted with the publication of the 1956 BEAR Report in June [4], nor was it even contrasted with the striking linearity recommendation of the Genetics Panel in press releases or news media stories.

Since the two Panels had differing charges and different scientific education/training, it is not surprising that they viewed the issue of mutation differently. These differing perspectives had long been apparent during high-level advisory committees where the medical perspective had been dominant due to the composition of the committee memberships. In fact, a principal tactic of the Rockefeller Foundation (RF), which funded the NAS BEAR activities, was to give the radiation geneticists a voice of their own, thereby quietly ensuring their (i.e. RF) goal that the LNT perspective would become policy. This suggestion is supported by the fact that Chairman Weaver and President Bronk selected geneticists that strongly supported LNT. This would prove to be a major stealth-like strategic decision by a non-governmental funding entity that changed the course of national and international governmental cancer risk assessment history. The action was greatly facilitated by the fact the President of the Rockefeller Institute for Medical Sciences (later renamed Rockefeller University) and the President of the US National Academy of Sciences was the same person, Dr. Detlev Bronk.

The NCRPM Committee (1958) (cited in 1960) [11] opted to use the linearity concept of the Genetics Panel for their recommendation for cancer risk assessment, even though cancer risk was in the domain of the Medical/Pathology Panel while germ cell risk was the focus of the Genetics panel.

The 1956 BEAR Genetics Panel would continue to function until 1964. The NAS Biological Effects of Ionizing Radiation (BEIR) would be re-formed in 1970 to address the issue of nuclear power, with James Crow, who had served on the previous BEAR Panels while chairing its final activities, becoming Chair of BEIR I, Genetics Subcommittee.

While vast attention was given to the 1956 Genetics Panel groundbreaking report, no such attention was given to their continuing efforts to address new scientific developments and concerns. Yet, the BEAR 1960 [2] report contained similarly significant independent recommendations by both the Genetics and Medical/Pathology Panels on predicting cancer risks in humans from low doses of ionizing radiation.

## 3. BEAR 1960 Genetics and Pathology Panels LNT recommednations

The recommendations for cancer risk assessment by the two Panels might have caught those who studied their 1956 reports by surprise. The two Panels arrived at the same conclusion that there were too many uncertainties and that cancer risk estimates could not be reliably done. In the words of the 1960 Medical/Pathology Panel [2]: "... the Committee does not consider it justifiable to predict human tumor incidences from small radiation doses based on extrapolation from the observed incidences following high dosage" (page 32). In the case of the 1960 Genetics Panel [2]: "We cannot say with any assurance whether the dose-response curve for induction of malignant disease is linear or non-linear at low levels." (page 10).

The converging statements of the two Panels in 1960 [2] represented a fundamental conclusion with major policy implications. It also represented major policy changes by both Panels from their positions in 1956. In the case of the Medicine/Pathology Panel there was a movement from strong support for a threshold model toward uncertainty. In the case of the Genetics Panel, their support for linearity for radiation induced gene mutation did not apply to radiation induced cancer risk assessment even though the mechanistic driver for many in the genetics community at this time was mutation. However, despite the importance of these conclusions, there was no fanfare, front page stories, reports sent to all public libraries, publications in *Science* or Congressional Hearings. The BEAR Genetics and Medical/Pathology Panel (1960) [2] activities seemed to have been intentionally relegated to secondary status, becoming a silent report. In subtle ways both Panel reports morphed to a position that supported the Precautionary Principle recommendation for cancer risk assessment by the NCRPM (1960) [11]. In retrospect, this was precisely what happened.

These joint 1960 BEAR Panel recommendations (i.e., Genetics and Medicine/Pathology) were ignored for the next 10 years, even by the Biological Effects of Ionizing Radiation (BEIR) I Genetics Subcommittee Report published in 1972 [5]. This 1972 BEIR report commented in detail on the 1956 Genetics Panel report, addressing significant changes since 1956, the most important being that of William Russell on dose rate, which the 1956 Genetics Panel admittedly got wrong. This is particularly important since the geneticist mantra was based on the belief that radiation induced mutation was not affected by dose rate and repair did not occur. This mistake was significant since the new Russell findings suggested the possibility of thresholds for mutation as well as for cancer risks. The Russell findings also signaled the existence of DNA repair, a suggestion that Edgar Altenburg shared with Hermann Muller within a few days of the Russell publication in letter correspondence [14].

While the BEIR I Genetics Subcommittee would struggle with the dose rate issue in its 1972 report [5], it is remarkable that this Genetics Subcommittee failed to address/comment on the 1960 BEAR Genetics and Medical/Pathology Panel [2] reports that high to low dose extrapolation for human ionizing radiation cancer risk was not scientifically justifiable. The reason(s) for this omission have never been probed in the literature.

The timing of the 1972 BEIR Report [5] was also critical, coming just two years after the creation of EPA. The 1972 BEIR Report indicated (page 51) that one of its principal goals was to provide EPA with the scientific basis for estimating risks at low levels of radiation exposure. In fact, in 1975 the EPA [1] announced that it was basing its cancer risk assessment upon the recommendations of the 1972 BEIR Report [5] with emphasis on the Russell et al. dose rate findings.

This is especially important since the 1972 subcommittee decided to "retain" the linearity recommendation of the 1956 Genetics Panel [3,4] even though the Russell data had shown a clear threshold for ionizing radiation induced mutation for oocytes at some 27,000 fold dose rate greater than background. However, no threshold had been observed for males, even though it was clear that dose rate was predominant and DNA repair was also quite substantial in the males but not quite as active as in the female. It was not known at that time that Russell's findings were in substantial error on the control group background mutation rate for male and female mice. These errors were corrected several decades later by the Russells, revealing that the females displayed an hormetic response whereas the males showed a threshold [15,16].

A principal question then is why didn't the 1972 BEIR I [5] Genetics Subcommittee address the convergent significant uncertainty conclusions of the 1960 BEAR Genetics and Medical Panels [2]. Since Crow was a member of all past Genetics committees/panels and chair of the 1962 Genetics Panel he had strong historical knowledge and context. Crow would also become an "unofficial" historian for the genetics community with many historical reflections. Thus, Crow would have had the historical presence and respect for such prior activities.

In 1960 it was known that dose rate was a central concept in genetics and that male and female mouse reproductive cells could repair mutations. Thus, the geneticist dogma of 1956 that all mutation damage was cumulative, non-reparable and irreversible had been effectively challenged and found to be largely incorrect by Russell. Also,



ED_002751_00030387-00002

other examples of ionizing radiation thresholds for mutation had been reported for other biological models at levels far greater than background doses [8,17].

## 4. A nascent EPA adopts LNT

These developments had the potential to suggest that a threshold model may be biologically more plausible than the LNT. Thus, while the statements of the 1960 BEAR Panels [2] seemed to provide a type of quiet cover or support to the NCRPM policy statement, this veiled support in the form of uncertainty was no longer sufficient (i.e. convincing enough). It is suggested here that the new Congressionally mandated environmental agency, the EPA, created in 1970, needed something better than regulation by uncertainty. The 1972 BEIR Report [5] provided EPA a basis (i.e., male mouse mutagenicity data) to support a linearity approach with the Russell data providing the Gold Standard and could be promoted in public as being based on studies using nearly two million mice. The 1972 BEIR [5] Report had the prerequisite caveats of some uncertainty and erring to some extent on the side of protection. However, the critical point was that now there was sufficient information for a science supported EPA linearity risk assessment policy that would soon have the apparent exacting precision of biostatistical model estimates of cancer risks in the low dose zone via the LNT approach. This historical evaluation suggests that the EPA did not want to have its hands tied or its scientific image affected by statements from the 1960 BEAR Genetics and Medicine Panels [2] that there was too much uncertainty to estimate cancer risk in the low dose zone. Their comments were simply ignored and swept under the regulatory rug.

## Funding

*This research received no specific grant from any* funding *agency in the public, commercial, or not-for-profit sectors.* EJC acknowledges longtime support from the U.S. Air Force (AFOSR FA9550-13-1-0047) and ExxonMobil Foundation (S18200000000256). The views and conclusions contained herein are those of the author and should not be interpreted as necessarily representing policies or endorsement, either expressed or implied. Sponsors had no involvement in study design, collection, analysis, interpretation, writing and decision to and where to submit for publication consideration.

## Declaration of interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cbi.2019.05.027.

## References

[1] United States Environmental Protection Agency (US EPA), Radiological Quality in the Environment of the United States, (1977) EPA 902/4-78-002.
[2] National Academy of Sciences (NAS), The Biological Effects of Atomic Radiation, Summary reports, Washington DC, 1960.
[3] Anonymous, Genetic panel, W. Weaver, chair), National Academy of sciences (NAS), biological effects of atomic radiation (BEAR), genetic effects of atomic radiation, Science 123 (1956) 1157–1164.
[4] National Academy of Sciences Biological Effects of Atomic Radiation, Medical/Pathology Panel, 1956.
[5] National Academy of Sciences (NAS)/National Research Council (NRC), The effects on populations of exposure to low levels of ionizing radiation, Report of the Advisory Committee on the Biological Effects of Ionizing Radiation, BEIR), December, 19721972.
[6] E.J. Calabrese, On the origins of the linear no-threshold (LNT) dogma by means of untruths, artful dodges and blind faith, Environ. Res. 142 (2015) 432–442.
[7] E.J. Calabrese, Origin of the linearity no threshold (LNT) dose-response concept, Arch. Toxicol. 87 (2013) 1621–1633.
[8] E.J. Calabrese, The road to linearity: why linearity at low doses became the basis for carcinogen risk assessment, Arch. Toxicol. 83 (2009) 203–225.
[9] G.F. Whittemore, The National Committee on Radiation Protection, 1929-1960: from Professional Guidelines to Government Regulation, Ph.D. Thesis (September) Department of the History of Science, Harvard University, Cambridge, MA, 1986.
[10] E.J. Calabrese, The linear no-threshold (LNT) dose response model: a comprehensive assessment of its historical and scientific foundations, Chem. Biol. Interact. 301 (2019) 6–25.
[11] National Committee on Radiation Protection and Measurement (NCRPM), Somatic radiation dose for the general population, Science 131 (1960) 482–486.
[12] W.L. Russell, L.B. Russell, E.M. Kelly, Radiation dose rate and mutation frequency, Science 128 (3338) (1958) 1546–1550.
[13] Anonymous, Pathologic effects of atomic radiation. Committee on pathologic effects of atomic radiation, Science 124 (3211) (1956) 60–63.
[14] E. Altenburg, Letter to Herman J. Muller, Lilly Library. University of Indiana. Muller Files., 1958, Accessed date: 27 December 1958.
[15] E.J. Calabrese, The threshold vs LNT showdown: dose rate findings exposed flaws in the LNT model part 1. The Russell-Muller debate, Environ. Res. 154 (2017) 435–451.
[16] E.J. Calabrese, The threshold vs LNT showdown: dose rate findings exposed flaws in the LNT model part 2, How a mistake led BEIR I to adopt LNT Environmental Research, 154 2017, pp. 452–458.
[17] E.J. Calabrese, Toxicology rewrites its history and rethinks its future, giving equal focus to both harmful and beneficial effects, Environ. Toxicol. Chem. 30 (2011) 2658–2673.



ED_002751_00030387-00003

Message

**From**: Edward Calabrese [edwardc@schoolph.umass.edu]
**Sent**: 11/7/2018 12:34:24 PM
**To**: Woods, Clint [woods.clint@epa.gov]
**Subject**: see interview

Clint:

See my interview on LNT.

Ed

https://youtu.be/YkJK34ffb30

Message

**From**: Jackson, Ryan [jackson.ryan@epa.gov]
**Sent**: 7/27/2018 5:32:37 PM
**To**: Yamada, Richard (Yujiro) [yamada.richard@epa.gov]
**Subject**: FW: DRAFT Letter to Administrator Wheeler Our Science Committee's Report Is Pivotal to Eliminating the Linear No-Threshold (LNT) Methodology
**Attachments**: ATT00001.txt; FINAL LNT Presentation of Howard McClintic.pptx; Final Agenda fo meeting with EPA on 6-14-18.docx

---

**From:** McClintic, Howard [mailto:McClintH@ctc.com]
**Sent:** Friday, July 27, 2018 12:24 PM
**To:** Jackson, Ryan <jackson.ryan@epa.gov>
**Subject:** FW: DRAFT Letter to Administrator Wheeler Our Science Committee's Report Is Pivotal to Eliminating the Linear No-Threshold (LNT) Methodology

I just left you a voicemail.

Let's discuss at your convenience.

Many thanks, most sincerely,

*Howard*

**Ex. 6 Personal Privacy (PP)**

---

**From:** McClintic, Howard
**Sent:** Tuesday, July 24, 2018 2:41 PM
**To:** Jackson.Ryan@EPA.gov
**Subject:** FW: DRAFT Letter to Administrator Wheeler Our Science Committee's Report Is Pivotal to Eliminating the Linear No-Threshold (LNT) Methodology

Did you see this email? Did someone from Murray Energy direct it to you?

Please share it with Administrator Wheeler.

Many thanks, most sincerely,

*Howard*

**Ex. 6 Personal Privacy (PP)**

---

**From:** McClintic, Howard
**Sent:** Thursday, June 14, 2018 4:15 PM
**To:** 'Jackson.Ryan@EPA.gov'

**Subject:** DRAFT Letter to Administrator Wheeler Our Science Committee's Report Is Pivotal to Eliminating the Linear No-Threshold (LNT) Methodology

***Ensuring the Future Through Innovation, Science and Technology***

2711 Jefferson Davis Hwy,, Suite 620
Arlington, VA 22202
**Ex. 6 Personal Privacy (PP)**
E-Mail: McClintH@ctc.com

Good Day Mr. Jackson,

My colleague, Dr. Robert (Bob) Golden and I were in headquarters last month, presenting some of the highlights of our LNT (linear no threshold) Project that is all about ***"transparency"*** and using ***cost-benefit analyses***. I believe that Administrator Wheeler respects not only Dr. Michael Honeycutt of Texas (who added pages 9 to 11 of the attachment), but also Dr. Edward Calabrese of Univ. of Massachusetts, who is the Co-Chair of the Science Committee.

I am sure that the Administrator would want to know about our Science Committee's Goals and Objectives as well as the importance and purpose of our soon to be completed peer-reviewed Report. The attached PowerPoint Presentation visually depicts in slides 7 through 11 the distortive effects of the LNT (linear no-threshold) methodology, when sharply contrasted with (and compared to) science-based data points. These slides underscore EPA Administrator Pruitt's central point that the mathematical construct that the EPA has been using for assessing risk, the linear no-threshold (LNT) methodology, is of **MOST** questionable scientific validity. The LNT model was originally adopted by the National Academy of Sciences (NAS) in 1956 for radiation and in 1977 for chemicals. Because LNT-driven regulations, whether for chemicals or

radiation, have, for many years, been claimed to be science-based (see (https://science.house.gov/sites/republicans.science.house.gov/files/documents/HHRG-113-SY-20131114-SD001%20.pdf as well as http://www.c-span.org/video/?327016-1/epa-administrator-gina-mccarthy-testimony-proposed-regulations), the underlying scientific foundation for such regulations, particularly the LNT model itself, should also, by definition, reflect empirical data. If such scientific data are lacking, as they are for the LNT model, science-based regulatory methodologies (including benefit-cost analyses) for both chemicals and radiation should be updated to reflect significant advancements in scientific knowledge.

Dr. Robert (Bob) Golden, and I would like to have either a Conference Call or Meeting with Administrator Wheeler or whoever he and you might suggest. soon. I am very grateful for your time, and attention – Thank You.

Most sincerely yours,

***Howard***

Howard G. McClintic
Executive Director
Ex. 6 Personal Privacy (PP)

**Comparison of the Scientific Basis of the Linear No Threshold (LNT) Model with Threshold Models for Cancer Risk Assessment of Radiation & Chemicals[a]**

| Chapters[a] | Author | Status |
|---|---|---|
| Prolog | Golden | Draft |
| Introduction | Bus | Draft |
| History of LNT | Calabrese | Final |
| The linear no-threshold model is less realistic than threshold or hormesis-based models: an evolutionary perspective | Costantini | Final |

| | | |
|---|---|---|
| The LNT model for cancer induction is not supported by radiobiological data | Scott | Final |
| The impact of dose-rate on LNT hypothesis for radiation risk assessment<br><br>Re-evaluation of the linear no-threshold (LNT) model using new paradigms and modern molecular studies<br><br>Threshold for low dose radon exposure | Brooks<br><br>Tharmalingam<br><br>Brooks | Final<br><br>Final<br><br>Final |
| Review of the evidence for thresholds for DNA-reactive and epigenetic experimental chemical carcinogens | Williams & Kobets | Draft |
| Mechanistic aspects of chemical carcinogens demonstrating thresholds | H Clewell & R Clewell | In progress |
| Epidemiological analysis of low dose/dose rate radiation exposure data | Ricci | Final |
| Economic implication of LNT vs. threshold models for benefit-cost analyses; formaldehyde & radon | Williams | Draft |
| Discussion, conclusions & recommendations | All | To be drafted |

a. Provisional titles

[1] https://www.nrc.gov/docs/ML1209/ML120970113.pdf

[1] Many areas in the world have natural background radiation levels higher than EPA's dose limits, natural background radiation in the United States is 30 times above the limit; Yangjiang, China, 60 times higher; Kerala coast, India, 100 times; and Ramsar, Iran, 2,000 times above the limit, without any adverse health effects. https://www.nrc.gov/docs/ML1209/ML120970113.pdf

This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

www.ctc.com 1-800-282-4392

# LNT Project

1. Introductions

2. Most of the Science Committee's papers are presently being reviewed by Roger McClellan, prior to their submission to ***Critical Reviews in Toxicology*** (see Table below). Following formal peer review, the collection of papers will constitute a special edition of this journal.

3. The outcome of this project will have major implications for EPA's regulatory programs -- evidence-based public policy determinations and heightened understanding of potential risks, posed by chemicals and radiation. As correctly stated by EPA Officials, regulations should be based on sound, high quality, transparent science. Notably, LNT does not fulfill any of these criteria. Modern molecular biology, for both radiation and chemicals, demonstrates numerous adaptive responses that continuously monitor and repair DNA.

4. The primary Goal of the Science Committee is to develop a high quality document with two objectives: to replace the use of the LNT model with science-based alternatives; and, to provide a thoughtful bases to publicize the economic distortions created by LNT-driven regulations. Additional benefits of our Report include:

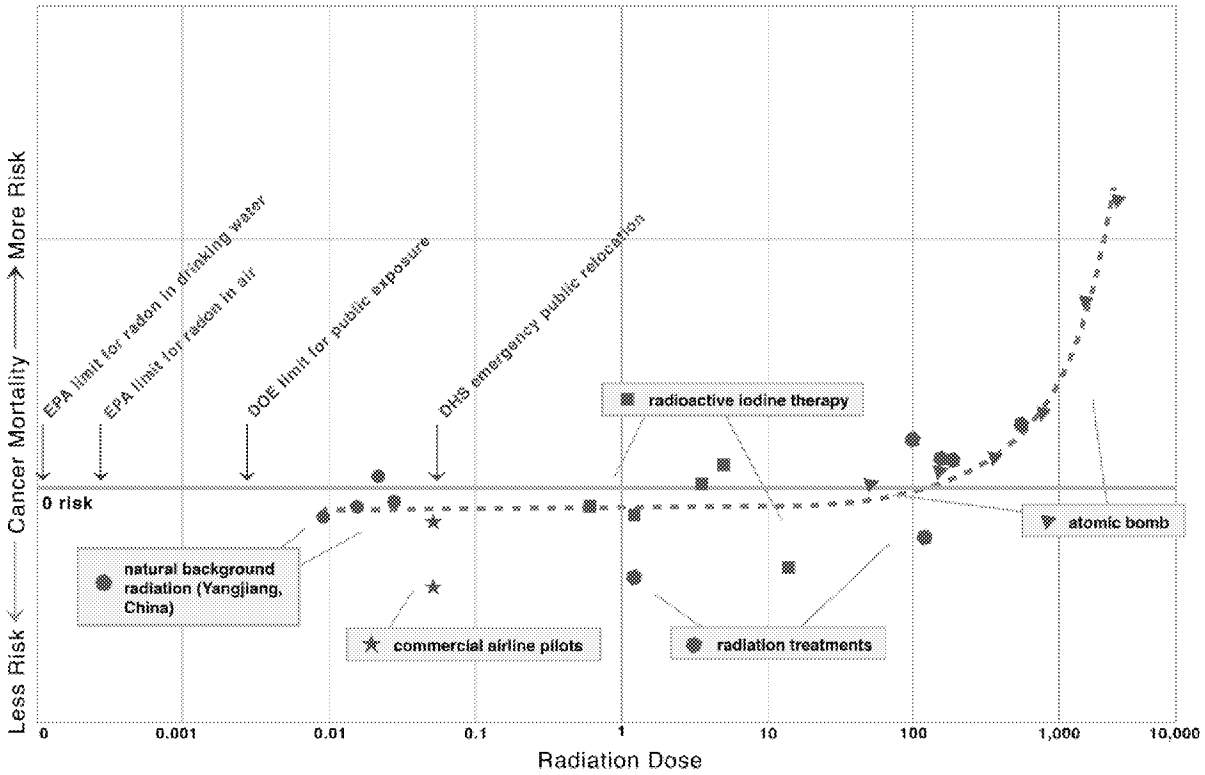
    a. Less resistance to the increased use of nuclear energy;
    b. Reduced unwarranted widespread fears of needed diagnostic imaging;
    c. Substantially reduced costs, potentially saving billions of dollars annually, to remediate chemical- or radiation-contaminated sites on EPA's/DOD's/DOE's Superfund lists, global implications;
    d. Directly challenge the likely conclusions of the next, eighth NAS Biological Effects of Ionizing Radiation (BEIR) Committee Report, which is virtually certain to once again endorse LNT despite its lack of biological validity;
    e. Epidemiology unable to detect a signal of harm spanning 5 orders of magnitude exposure as shown in the graphic below; and,
    f. As also illustrated in the graphic, at less than 100 mSv, because there is no detectable increase in cancer, which represents a clear threshold.

5. Next Steps

6. Conclusions and Thanks



ED_002751_00031449-00001




Vertical axis indicates excess relative risk compared to zero; x axis is in millisieverts per day (mSv/d)
EPA, DOE and DHS dose limits expressed in mSv/day based on cumulative limit per year

Red arrows indicate EPA, DOE, and DHS regulatory limits.[i] The DHS trigger for emergency mass relocation is over *1,000 times below* the threshold of harm – pegged at about the same radiation dose received by longer-lived airline pilots. Vastly expensive EPA regulations requiring radon cleanup of air and water are triggered at dose levels approaching *1 million times* below the threshold.[ii]

**Comparison of the Scientific Basis of the Linear No Threshold (LNT) Model with Threshold Models for Cancer Risk Assessment of Radiation & Chemicals[a]**

| Chapters[a] | Author | Status |
|---|---|---|
| Prolog | Golden | Draft |
| Introduction | Bus | Draft |
| History of LNT | Calabrese | Final |
| The linear no-threshold model is less realistic than threshold or hormesis-based models: an evolutionary perspective | Costantini | Final |
| The LNT model for cancer induction is not supported by radiobiological data | Scott | Final |
| The impact of dose-rate on LNT hypothesis for radiation risk assessment | Brooks | Final |
| Re-evaluation of the linear no-threshold (LNT) model using new paradigms and modern molecular studies | Tharmalingam | Final |
| Threshold for low dose radon exposure | Brooks | Final |
| Review of the evidence for thresholds for DNA-reactive and epigenetic experimental chemical carcinogens | Williams & Kobets | Draft |
| Mechanistic aspects of chemical carcinogens demonstrating thresholds | H Clewell & R Clewell | In progress |
| Epidemiological analysis of low dose/dose rate radiation exposure data | Ricci | Final |
| Economic implication of LNT vs. threshold models for benefit-cost analyses; formaldehyde & radon | Williams | Draft |
| Discussion, conclusions & recommendations | All | To be drafted |

a. Provisional titles

---

[i] https://www.nrc.gov/docs/ML1209/ML120970113.pdf

[ii] Many areas in the world have natural background radiation levels higher than EPA's dose limits, natural background radiation in the United States is 30 times above the limit; Yangjiang, China, 60 times higher; Kerala coast, India, 100 times; and Ramsar, Iran, 2,000 times above the limit, without any adverse health effects. https://www.nrc.gov/docs/ML1209/ML120970113.pdf



ED_002751_00031449-00003

Message

**From**: Bennett, Tate [Bennett.Tate@epa.gov]
**Sent**: 10/25/2017 7:47:08 PM
**To**: Yamada, Richard (Yujiro) [yamada.richard@epa.gov]
**Subject**: FW: Letter of Support
**Attachments**: Letter of Support for HR 4012 - 87 Experts.pdf

---

**From:** Clint Woods [mailto:cwoods@csg.org]
**Sent:** Wednesday, October 18, 2017 3:00 PM
**To:** Bennett, Tate <Bennett.Tate@epa.gov>
**Subject:** Letter of Support

June 23, 2014

The Honorable Lamar Smith, Chairman
House Committee on Science, Space, and Technology
2321 Rayburn House Office Building
Washington, D.C 20515

Dear Chairman Smith,

We write in support of the principles contained in H.R. 4012, the Secret Science Reform Act. This legislation supports a basic tenet: the Environmental Protection Agency's regulations should be based on transparent and reproducible science.

Potentially costly regulations should be grounded in data and analyses that are available to academic, government, and independent scientists. Pushing EPA to ensure that the data, models, and methods it relies on are open to public and scientific scrutiny will make the Agency's regulations more accountable, credible, and enforceable.

While we hail from a variety of scientific and academic disciplines, we agree that the provisions of this legislation could be satisfied by EPA without difficulty. The bill is also consistent with recent trends toward access among major scientific journals across these fields. Transparency and reproducibility in EPA regulatory science will encourage more robust analysis of findings by investigators with diverse perspectives while allowing the Agency to base its policy decisions on the best available science. Complying with H.R. 4012 can be accomplished without imposing unnecessary burdens, discouraging research, or raising confidentiality concerns. Across different disciplines, numerous statistical and technical approaches exist to protect any sensitive information.

We support passage of this legislation and thank your Committee for its leadership on this important issue.

Sincerely,



ED_002751_00031472-00001

Dr. Charles A. Ager, PhD
Founder and Chairman, Nanominerals Corp

Dr. Ralph B. Alexander, PhD
Former Associate Professor, Physics, Wayne State University

Mr. Robert A. Ashworth
Chemical Engineer

Dr. Charles R. Anderson, PhD
President and Principal Scientist, Anderson Materials Evaluation, Inc.

Dr. J. Scott Armstrong, PhD
Professor, Marketing, Wharton School, University of Pennsylvania

Dr. James R. Barrante, PhD
Professor Emeritus, Physical Chemistry, Southern Connecticut State University

Dr. Charles Battig, M.D.
President, Piedmont Chapter, Virginia Scientists and Engineers for Energy and Environment

Dr. Denis Beller, PhD
Research Professor, Nuclear Engineering, University of Nevada Las Vegas

Dr. David J. Benard, PhD
Physicist (ret.)

Dr. Michael A. Berry, PhD
Former Deputy Director, National Center for Environmental Assessment, USEPA (ret.) and
Research Professor, Environmental Sciences, University of North Carolina at Chapel Hill

Dr. Charles A. Berst, PhD
Emeritus Professor, English, University of California, Los Angeles

Dr. William M. Briggs, PhD
Statistical Consultant and Adjunct Professor of Statistical Science, Cornell University

Dr. Edward Calabrese, PhD
Professor, Environmental Health Sciences, University of Massachusetts Amherst



ED_002751_00031472-00002

Dr. Angelo J. Campanella, PhD
Principal, Campanella Acoustics

Dr. Alan Carlin, PhD
Senior Operations Research Analyst, USEPA (ret.)

Dr. Lawrence M. Cathles, PhD
Professor, Geological Sciences, Cornell University

Dr. Charles R. Christensen, PhD
Research Physicist, Retired from Weapon Sciences Directorate, US Army Aviation and Missile Command.

Dr. Dustin Chambers, PhD
Associate Professor, Economics, Salisbury University

Dr. Michael S. Coffman, PhD
President, Environmental Perspectives, Inc.

Dr. Roger Cohen, PhD
Fellow, American Physical Society

Dr. William F. Condon, PhD
Emeritus Professor, Chemistry, Southern Connecticut State University

Dr. Louis Anthony Cox, Jr., PhD
Chief Sciences Officer, Next Health Technologies; Clinical Professor, Biostatistics and Informatics, University of Colorado Health Sciences Center; and President, Cox Associates

Dr. James Crosswell, MD
Physician

Dr. Tim Davis, PhD
Licensed Specialist Clinical Social Worker

Dr. Ulrich Decher, PhD
Adjunct Faculty, University of Hartford

Dr. Arthur Desrosiers, ScD
Environmental Health Physicist



ED_002751_00031472-00003

Dr. Pamela C. Dodds, PhD
Registered Professional Geologist

Dr. Harold H. Doiron, PhD
Chairman, The Right Climate Stuff Research Team

Dr. Nicholas Drapela, PhD
Former Professor, Chemistry, Oregon State University

Mr. John Droz, Jr.
Physicist and Executive Director of the Alliance for Wise Energy Decisions

Mr. John Dale Dunn, MD, JD
Consultant Emergency Services/Peer Review, Civilian Faculty, Emergency Medicine Residency, Carl R. Darnall Army Medical Center, Fort Hood

Dr. James E. Enstrom, PhD
Researcher (ret.), School of Public Health, University of California, Los Angeles and President, Scientific Integrity Institute

Dr. Dan Ervin, PhD
Professor, Finance, Perdue School of Business, Salisbury University

Dr. Irvin H. Forbing, DDS
Dentist

Dr. Patrick Frank, PhD
Research Chemist

Dr. Gordon J. Fulks, PhD
Astrophysicist

Dr. Laurence I. Gould, PhD
Professor, Physics, University of Hartford

Dr. Shawn Grannell, PhD
Inventor



ED_002751_00031472-00004

Dr. William M. Gray, PhD
Professor Emeritus, Department of Atmospheric Science, Colorado State University

Dr. Tim Groseclose, PhD
Professor, American Politics and Public Policy, University of California, Los Angeles

Dr. William Happer, PhD
Professor, Physics, Princeton University

Dr. Victor Davis Hanson, PhD
Senior Fellow, Hoover Institution at Stanford University

Dr. Doug L. Hoffman, PhD
Former Research Professor, Computer Science, University of North Carolina at Chapel Hill

Dr. Albert Kris Huber, PhD
Electrical Engineer

Dr. W. Reed Johnson, PhD
Professor Emeritus, Nuclear Engineering, University of Virginia

Dr. Jason S. Johnston, PhD
Professor of Law, University of Virginia

Mr. Brian T. Kennedy
President, The Claremont Institute

Dr. E. Christian Kopff, PhD
Associate Professor, Classics, University of Colorado, Boulder

Dr. Patricia A. Lapoint, PhD
Professor, Management, McMurry University

Dr. Lubert Leger, PhD
Former Assistant Chief, Materials Division, Engineer Directorate, Johnson Space Center, NASA

Dr. Jay Lehr, PhD
Science Director, The Heartland Institute



ED_002751_00031472-00005

Dr. Jonathan A. Lesser, PhD
President, Continental Economics

Dr. Richard E. Lindstrom, PhD
Professor Emeritus, University of Connecticut

Dr. Anthony Lupo, PhD
Professor, Atmospheric Science, University of Missouri

Dr. Matthew A. Malkan, PhD
Professor, Physics and Astronomy, University of California, Los Angeles

Dr. Martin J. Mangino, PhD
Professor, Surgery, Virginia Commonwealth University

Dr. Calvin Luther Martin, PhD
Associate Professor of History (ret.), Rutgers University

Dr. John Martinis, PhD
Professor, Physics, University of California, Santa Barbara

Dr. Robert J. Michaels, PhD
Professor, Economics, California State University, Fullerton

Dr. Henry I. Miller, M.D.
Robert Wesson Fellow in Scientific Philosophy and Public Policy, Hoover Institution at Stanford University

Dr. Ferenc M. Miskolczi, PhD
Former Senior Principal Scientist, NASA Langley Research Center

Dr. Dennis M. Moltz, PhD
Owner, High Desert Nuclear Technologies

Dr. Michael Newton, PhD
Professor Emeritus, Forest Ecology, Oregon State University

Dr. Helen Schwiesow Parker, PhD
Licensed Clinical Psychologist



ED_002751_00031472-00006

Dr. Nina Pierpont, MD, PhD
Former Clinical Professor of Pediatrics, College of Physicians and Surgeons, Colombia University; currently a pediatrician in private practice

Dr. Jerry L. Punch, PhD
Professor Emeritus, Department of Communicative Sciences and Disorders, Michigan State University

Dr. Forrest J. Remick, PhD
Emeritus Professor, Nuclear Engineering, and Emeritus Associate Vice President, Research, The Pennsylvania State University; and Commissioner (Retired), US Nuclear Regulatory Commission

Dr. James H. Rust, PhD
Professor of Nuclear Engineering (ret.), Georgia Tech

Mr. Donald F. Shaw, Sr.
Senior Engineering Advisor

Dr. Thomas Sheahen, PhD, PE
Physicist

Dr. S. Fred Singer, PhD
Professor Emeritus, Environmental Science, University of Virginia, and Director, Science and Environmental Policy Project

Dr. Thomas L. Steepy, PhD
Plant Pathologist

Dr. Gary Steinberg, DMD
Dentist

Dr. Glenda Tannahill, PhD
CEO/CFO, Good Samaritan

Dr. George S. Taylor, PhD
Director, Palmetto Energy Institute

Dr. David E. Thompson, PhD
Founder and President, Metric Echo, Inc, and Dean Emeritus, College of Engineering, University of Idaho



ED_002751_00031472-00007

Dr. Marc Trachtenberg, PhD
Professor, Political Science, University of California, Los Angeles

Dr. Michael Trigoboff, PhD
Instructor, Computer Science, Portland Community College

Dr. Stanley W. Trimble, PhD
Professor Emeritus, Department of Geography, UCLA

Dr. Kirby Tyndall, PhD
Environmental Toxicologist

Dr. James Wanliss, PhD
Associate Professor, Physics, Presbyterian College

Dr. Robert Whitsett, PhD
Former Staff Scientist, Lawrence Berkeley National Laboratory

Dr. Charles Wolf, Jr., PhD
Distinguished Chair in International Economics, RAND Corporation and Professor, Pardee RAND Graduate School

Dr. George T. Wolff, PhD
Principal Scientist, Air Improvement Resource, Inc.; Former Chair, EPA Clean Air Scientific Advisory Committee

Dr. Peter W. Wood, PhD
President, National Association of Scholars

Dr. Steven B. Young, PhD
Former Professor of Biology, Middlebury University

Dr. S. Stanley Young, PhD
Assistant Director for Bioinformatics, National Institute of Statistical Sciences

cc: Eddie Bernice Johnson, Ranking Member, House Committee on Science, Space, and Technology



ED_002751_00031472-00008

Message

**From**: Yamada, Richard (Yujiro) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C34A1E0345E4D26B361B5031430639D-YAMADA, YUJ]
**Sent**: 2/14/2018 5:33:22 PM
**To**: Konkus, John [konkus.john@epa.gov]
**Subject**: Re: Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!

**Ex. 5 Deliberative Process (DP)** .. thanks john, hope all is going well otherwise!

Sent from my iPad

On Feb 14, 2018, at 11:41 AM, Konkus, John <konkus.john@epa.gov> wrote:

**Ex. 5 Deliberative Process (DP)**

**From:** McClintic, Howard [mailto:McClintH@ctc.com]
**Sent:** Wednesday, February 14, 2018 11:36 AM
**To:** Konkus, John <konkus.john@epa.gov>
**Subject:** FW: Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!
**Importance:** High

Good Day Mr. Konkus,

Dr. Golden and I would like to talk to you and/or "whoever" you might suggest about this Project – when might that be possible?

Dr. Michael Honeycutt, Chair of the SAB, endorses this Project and helped me with my PowerPoint slides. Mr. Pruitt and he are friends, as is Dr. Ed Calabrese, a Co-Chair of the Project.

Many thanks, most sincerely,

***Howard***

**Ex. 6 Personal Privacy (PP)**

---

**From:** Konkus, John [mailto:konkus.john@epa.gov]
**Sent:** Wednesday, February 14, 2018 11:01 AM
**To:** McClintic, Howard
**Subject:** Read: Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!
**Importance:** High

Your message

To:

Subject: Saving Hundreds of Millions of Dollars Remediating Superfund Sites -- Get Rid of the LNT!
Sent: Wednesday, February 14, 2018 11:01:38 AM (UTC-05:00) Eastern Time (US & Canada)

was read on Wednesday, February 14, 2018 11:01:00 AM (UTC-05:00) Eastern Time (US & Canada).

This message and any files transmitted within are intended solely for the addressee or its representative and may contain company sensitive information. If you are not the intended recipient, notify the sender immediately and delete this message. Publication, reproduction, forwarding, or content disclosure is prohibited without the consent of the original sender and may be unlawful.

Concurrent Technologies Corporation and its Affiliates.

www.ctc.com 1-800-282-4392

Message

**From**: Yamada, Richard (Yujiro) [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=4C34A1E0345E4D26B361B5031430639D-YAMADA, YUJ]
**Sent**: 8/23/2017 5:19:06 PM
**To**: Zarba, Christopher [Zarba.Christopher@epa.gov]
**Subject**: one more for SAB consideration

Ex. 5 Deliberative Process (DP)

Thanks Chris, Richard

Richard Yamada
Deputy Assistant Administrator
Office of Research and Development
U.S. Environmental Protection Agency

Phone: Ex. 6 Personal Privacy (PP)
yamada.richard@epa.gov