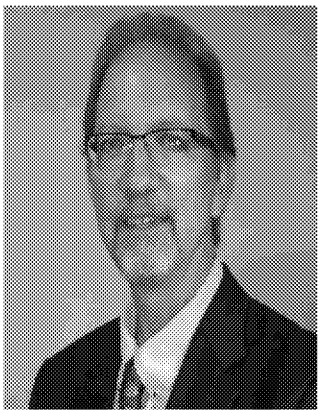
Understanding the Basic and Application of Risk Assessment

John Vandenberg, PhD

January 31, 2019

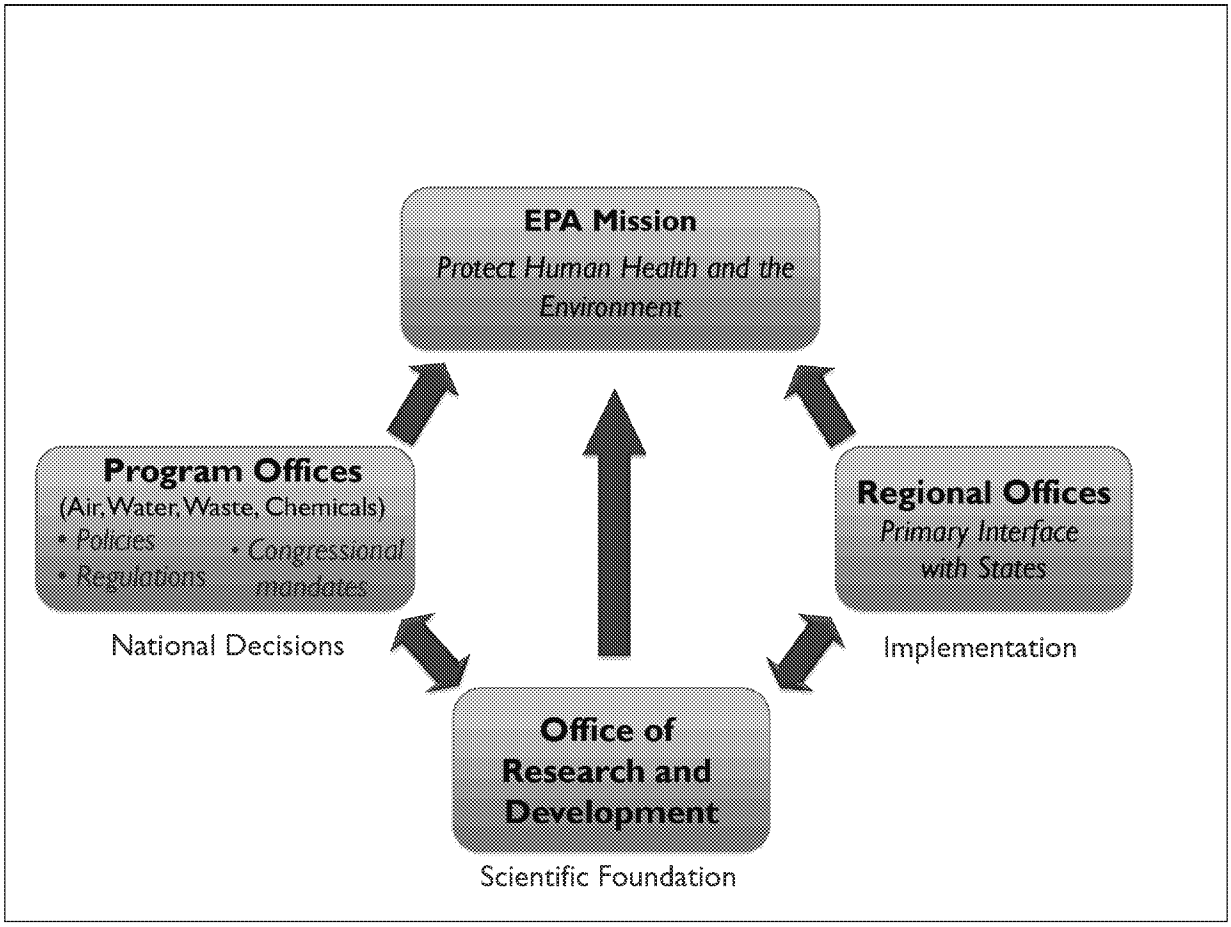
The Speaker

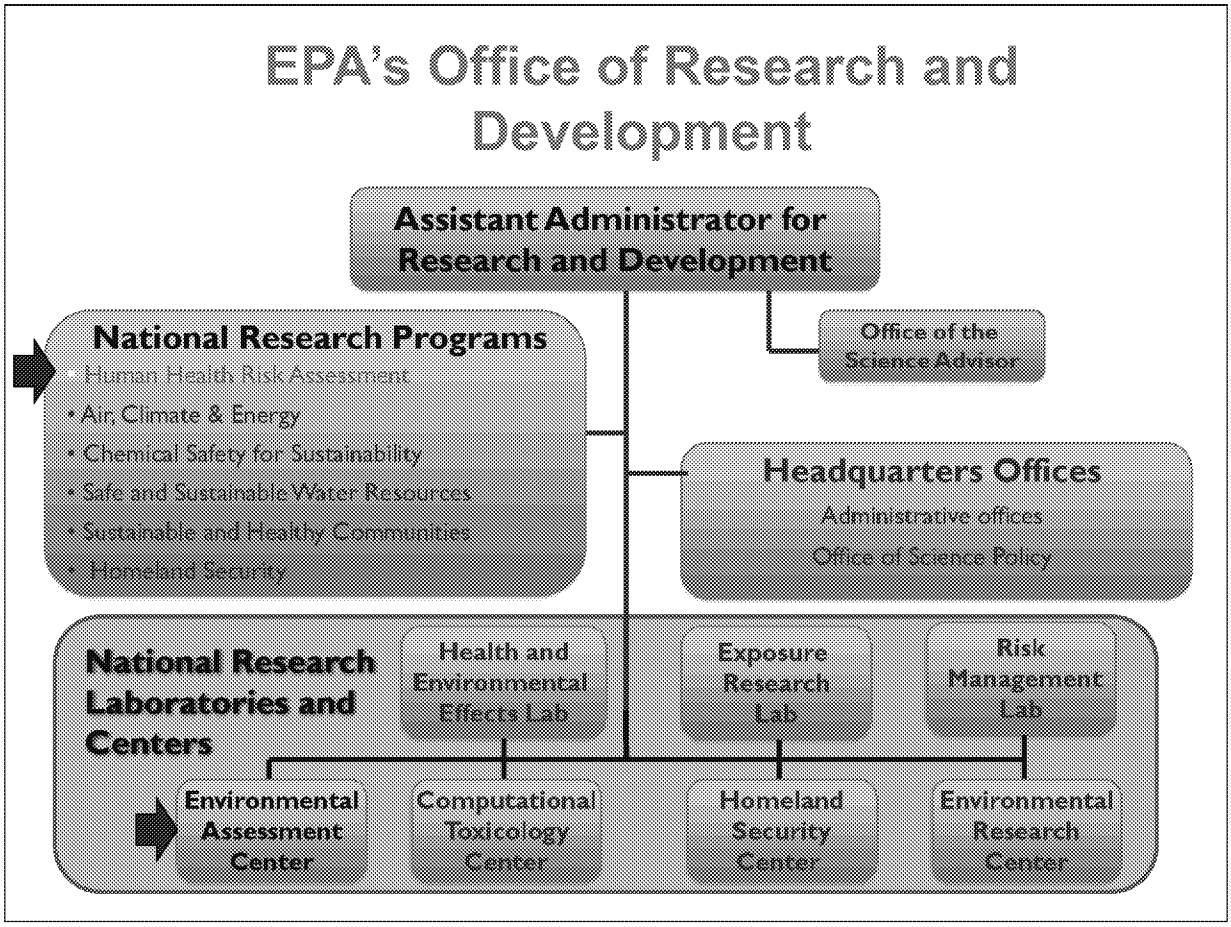


John Vandenberg, PhD

- Director of NCEA-RTP 75 staff
- 30+ years risk assessment experience
- US EPA National Center for Environmental Assessment
- Adjunct Professor, Nicholas School of the Environment, Duke University;
- Teaches graduate course on Air Quality Management and previously on health risk assessment
- Europe, South America, Africa, Southeast Asis training on principles and applications of toxicological research and risk assessments

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

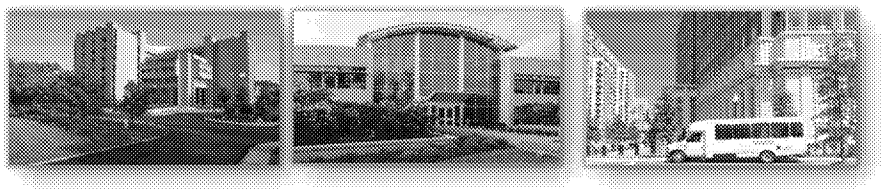

EPA Mission
Protect Human Health and the Environment
Program Offices
(Air, Water, Waste, Chemicals)
• Policies
• Regulations
• Congressional mandates
National Decisions
Regional Offices
Primary Interface with States
Implementation
Office of Research and Development
Scientific Foundation


EPA's Office of Research and Development
Assistant Administrator for Research and Development
Office of the Science Advisor
National Research Programs
• Human Health Risk Assessment
• Air, Climate & Energy
• Chemical Safety for Sustainability
• Safe and Sustainable Water Resources
• Sustainable and Healthy Communities
• Homeland Security
Headquarters Offices
Administrative offices
Office of Science Policy
National Research Laboratories and Centers
Health and Environmental Effects Lab
Exposure Research Lab
Risk Management Lab
Environmental Assessment Center
Computational Toxicology Center
Homeland Security Center
Environmental Research Center

HSR 101

National Center for Environmental Assessment (NCEA)

- The mission of NCEA is to provide guidance (assessments and guidelines) about how pollutants may impact human health and the environment.
- NCEA occupies a critical position between scientists in ORD and management in EPA's program and regional offices supporting regulatory, enforcement, and remedial-action decisions.
- NCEA administers three high-profile programs: the Global Change Research Program, the Report on the Environment (ROE Database), Integrated Science Assessment (ISA) and the Integrated Risk Information System (IRIS) Program & Database.
- NCEA's diverse staff includes biologists, chemists, ecologists, engineers, epidemiologists, geneticists, statisticians, and toxicologists.



Student Activity

How would you define hazard?

How would you define risk?

How would you define risk assessment?

When someone tries to identify hazard or risk, many issues may come in mind such as:

Qualitative or quantitative
Hazard, stressor, agent, chemical
Estimate, probability
Uncertainty, variability
Adverse effect, outcome, health endpoint
Scientifically based

Simply, these terms can be defined as:
Hazard is a potential source of harm
Risk is the probability of adverse effects resulting from exposure to a hazard
Risk Assessment is assessing the probability of adverse effects resulting from exposure to a hazard. Later in the course you will learn the EPA definition for Hazard, Risk and Risk Assessment

Student Activities

- Hazards and Risks

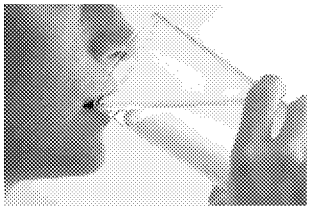
- https://www.youtube.com/watch?v=n_IPD1ZMXpA

To further understand the concept of hazards and risks, please watch this video from youtube

For a Risk to Occur…

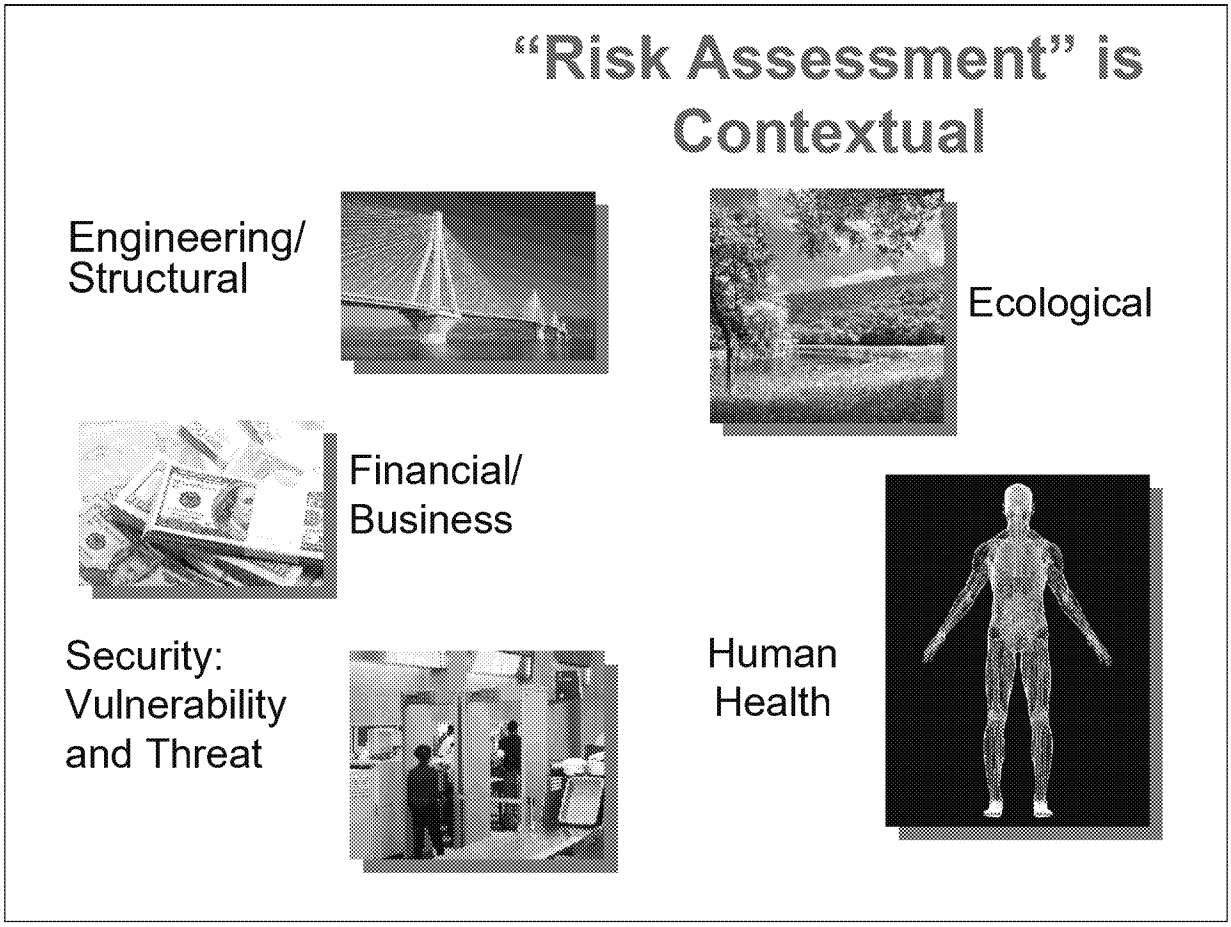
1. A hazard <u>must</u> exist, and

2. Exposure <u>must</u> take place



Question for the student?

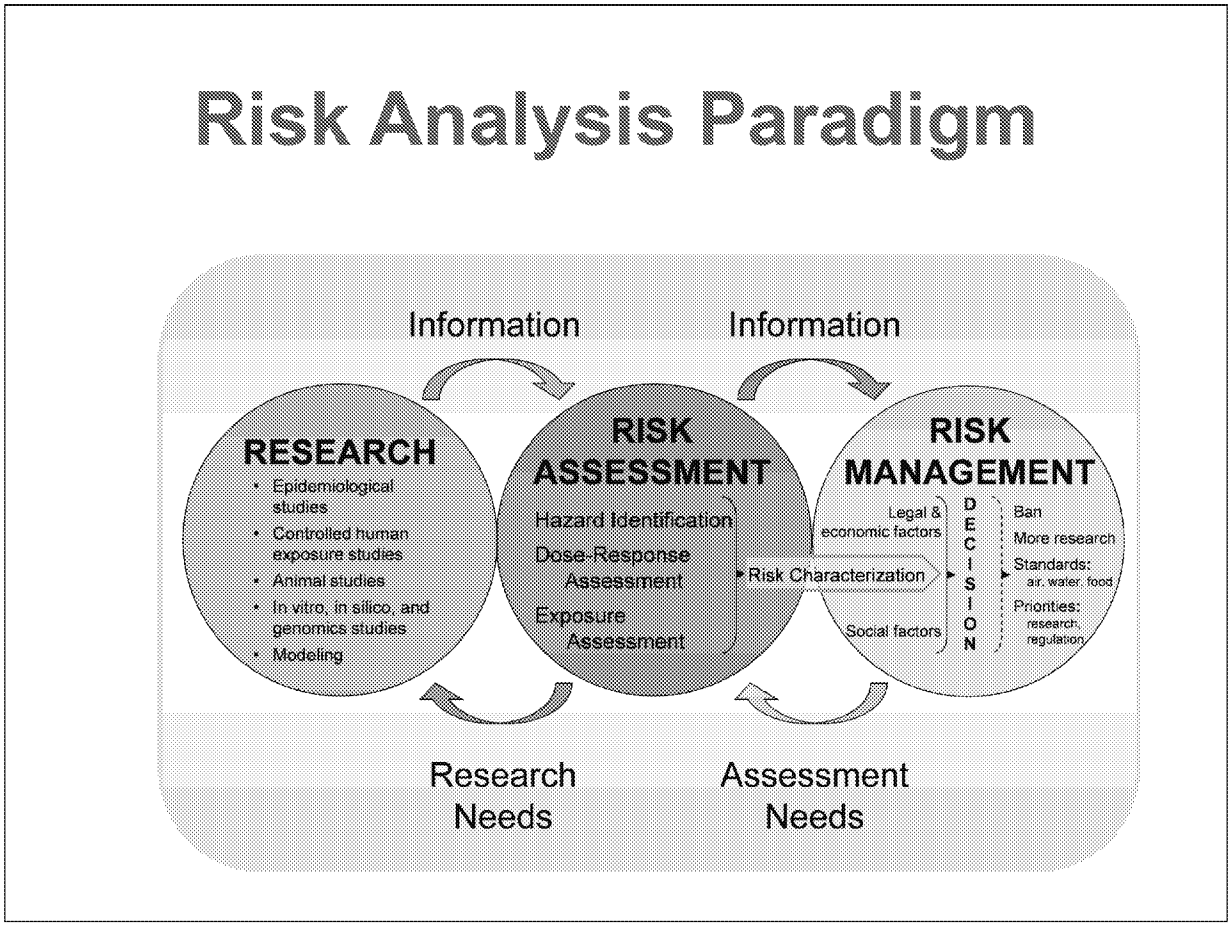
Can you think of any other hazard/risk scenarios? – they can be chemical, biological, physical, or natural.
Exposure to the hazard is essential to induce the risk.



The field of Risk Assessment can cover almost any aspect of life.

The term risk assessment is used in multiple contexts:
Engineering/structural
Financial/business
Security – vulnerability and threat assessment
Ecological
Human health
Physical injury
Radiation
Microbial
Chemical

Because risk assessment is contextual, the definition can vary by context. The context of this course is human health risk assessment, primarily focused on chemical risk assessment, and so the definitions that we will discuss are presented from this perspective.



These paradigms are specific to human health risk assessment.
Risk assessment can be viewed as part of a broader "risk analysis" paradigm. The other two components are:
Research including epidemiology research, clinical studies, animal studies, in vitro, in vivo and modeling.
Risk management which covers regulatory (or other) decision-making.
Some people also include risk communication which covers effectively communicating the results of risk assessment and the policy implications of risk management decisions.

Within the risk assessment circle, the four basic components of risk assessment are listed (according to the 1983 NRC red book).
Hazard Identification
Dose-response Assessment
Exposure Assessment
Risk Characterization

Two other recent additions to the risk assessment paradigm are
Stakeholder involvement – emphasis on stakeholder involvement through all phases of risk assessment. This includes internal and external stakeholders, and
Problem formulation and scoping – emphasizes thinking through the possible risk management options before beginning the risk assessment. This is a necessary step in order to decide what information should be collected during the actual risk assessment.

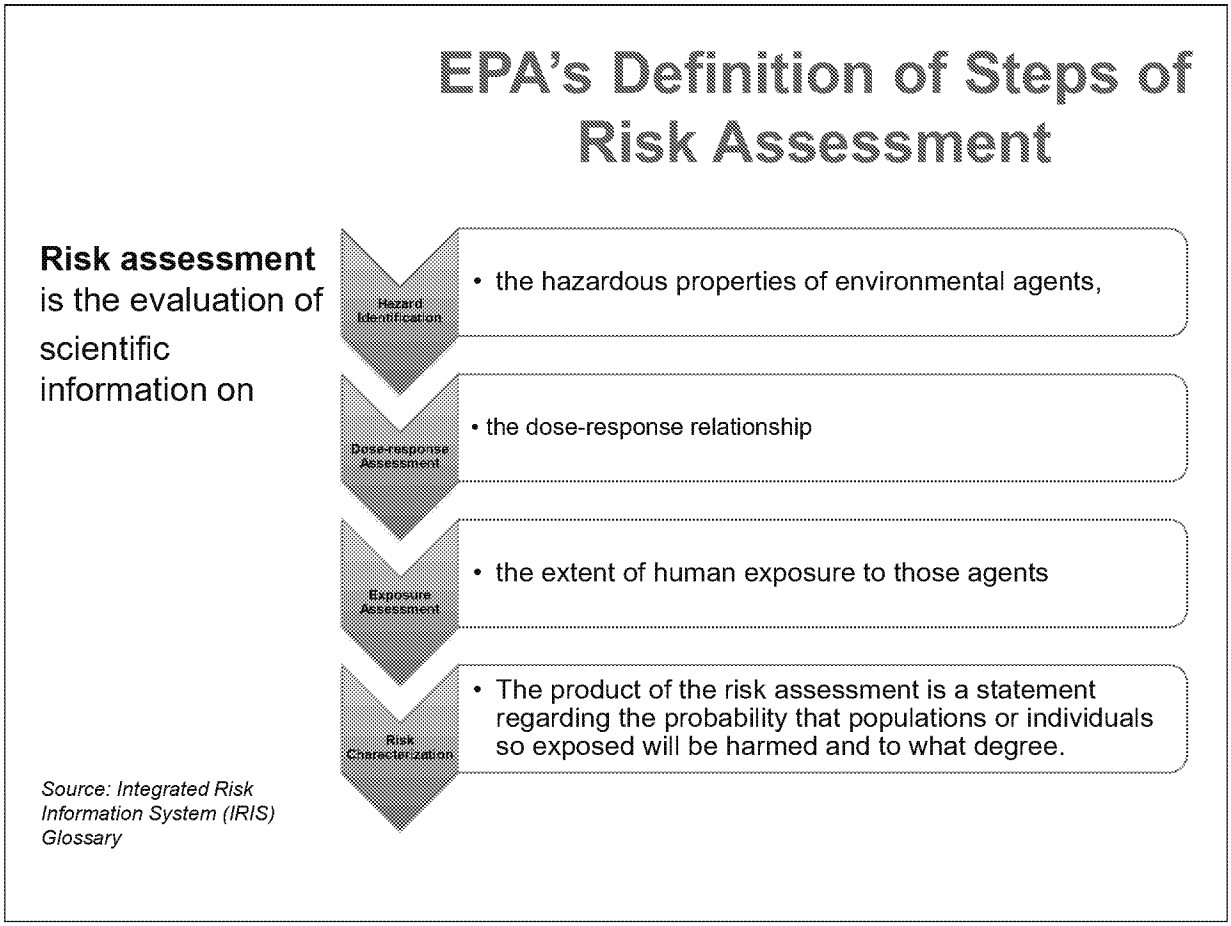
EPA Definition of Risk Assessment

Risk assessment:

Qualitative and quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence and/or use of specific pollutants

From EPA's "Terms of Environment" Glossary

This is a general definition from EPA's "Terms of Environment" glossary:
It says, "Risk assessment is a qualitative and quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence and/or use of specific pollutants."
An important concept to understand is that "risk" typically refers to the probability, or likelihood, that something might happen in the future. From the Terms of the Environment glossary, risk is "a measure of the probability that damage to life, health, property, and/or the environment will occur as a result of a given hazard."
An evaluation of the current rate of disease within a population is not risk assessment; this is better described as epidemiology.
It is also important to know that risk assessment is used as a verb describing the process and also as a noun, describing the document that results from doing a risk assessment. In this course, we will typically use risk assessment as a verb.
For student reference:
This is a periodically-updated glossary of common terms; it can be found at http://www.epa.gov/glossary/.



A second, expanded definition of risk assessment can be found in EPA's Glossary of IRIS Terms. IRIS is EPA's Integrated Risk Information System; it is an important data base of toxicity information that NCEA developed and maintains.
This definition is based on the 4 components of the risk assessment paradigm developed by the National Research Council or NRC.
Risk assessment, in terms of human health, is the evaluation of scientific information on:
the hazardous properties of environmental agents (This is hazard identification, and IRIS assessments include hazard identification.),
the dose-response relationship (This is dose-response assessment and is also included in IRIS assessments.), and
the extent of human exposure to those agents (This is exposure assessment.).
The product of the risk assessment is a statement regarding the probability that populations or individuals so exposed will be harmed and to what degree (This is the risk characterization component of the National Research Council's paradigm). Risk characterization synthesizes the information collected and evaluated in the other three steps.
An analogous and similar (but not identical) definition exists for ecological risk assessment.
There is variation among federal agencies regarding the conduct of risk assessment, but the overarching frameworks that Agencies use are based on the NRC paradigm. Details can differ based on statutory requirements and history of practice within the agency.

WHO Definition of Risk Assessment

Risk assessment:

Human health risk assessment is a process intended to estimate the risk to a given target organism, system or (sub)population, including the identification of attendant uncertainties, following exposure to a particular agent, taking into account the inherent characteristics of the agent of concern as well as the characteristics of the specific target system (IPCS, 2004).

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It says, "Risk assessment is a qualitative and quantitative evaluation of the risk posed to human health and/or the environment by the actual or potential presence and/or use of specific pollutants."
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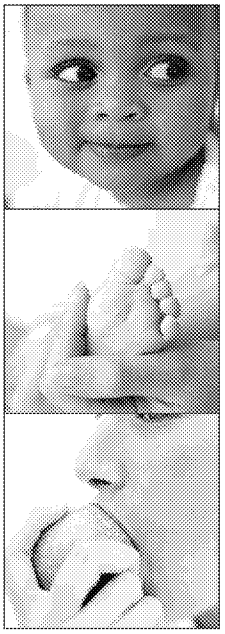
Risk Assessment is Critical to Regulatory Decision-Making

- U.S. EPA is both a regulatory agency and a science agency
- U.S. EPA operates under many laws that require the assessment of potential risk from exposure to environmental contaminants
- Risk assessment remains fundament to major programs in the Agency (water, air, waste)
- Risk assessment evolves with advancement in science



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The Vinyl Chloride Story

- 1970: EPA established
- Most vinyl chloride is used to make polyvinyl chloride (PVC) plastic and vinyl products.
- Reports of cases of liver cancer (many resulting in death) in workers at vinyl chloride facilities were reported in the media in the early 1970s. Some cases of angiosarcoma were reported in people who lived in the vicinity of facilities producing vinyl chloride.
- 1975: First EPA chemical assessment (vinyl chloride)
- OSHA lowered permissible levels protecting workers, and EPA assessed the need to limit emissions of vinyl chloride into the air from these facilities.
- EPA published the "Quantitative Risk Assessment for Community Exposure to Vinyl Chloride."
- Current OSHA is 1 ppm . 5 ppm [15-minute]
- Followed in 1976 by "Interim Procedures and Guidelines for Health Risk and Economic Impact Assessments of Suspected Carcinogens" published by EPA Administrator (these were not formal guidelines or policy, but were the beginnings of such guidelines)

EPA was established in 1970.
EPA completed its first risk assessment document in December 1975.
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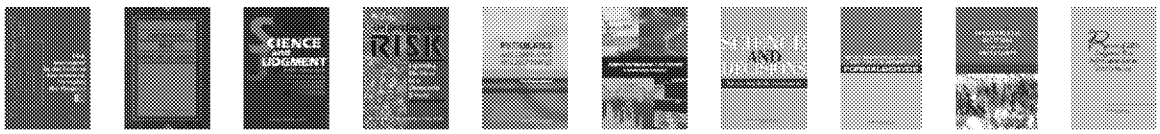
National Research Council (NRC) publications on risk assessment

- 1983: *Managing the Process* – the "Red Book"
- 1989: *Improving Risk Communication*
- 1994: *Science and Judgment* – the "Blue Book"
- 1996: *Understanding Risk*
- 2007: *Toxicity Testing in the 21st Century*
- 2008: *Phthalates and Cumulative Risk Assessment*
- 2009: *Science and Decisions* – the "Silver Book"
- 2011: Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde
- 2013: Environmental Decisions in the Face of Uncertainty
- 2014: Review of EPA's Integrated Risk Information System (IRIS) Process



Between 1983 and 2009, the National Research Council (a part of the National Academy of Sciences) published several documents that are key to risk assessment.
The first book, published in 1983 was titled Risk Assessment in the Federal Government: Managing the Process. You may hear it referred to as the "Red Book" because of the color of its cover.
NRC was commissioned by Congress to prepare this set of recommendations
Book contains definitions and fundamental processes still in use today
This book introduced the risk assessment paradigm with its four traditional components:
Hazard Identification
Dose-response Assessment
Exposure Assessment
Risk Characterization
1994 - Science and Judgment in Risk Assessment, aka the "Blue Book"
Also commissioned by Congress (via Clean Air Act)
In part, a follow-up to the Red Book, but with specific emphasis on EPA's scientific methods
2009 - Science and Decisions: Advancing Risk Assessment, aka the "Silver Book"
Discusses the planning and scoping principles of risk assessment along with stakeholder involvement, with EPA in mind
Other NRC publications on risk assessment include:
1989: Improving Risk Communication
1996: Understanding Risk
2007: Toxicity Testing in the 21st Century
2008: Phthalates and Cumulative Risk Assessment
2011: Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde
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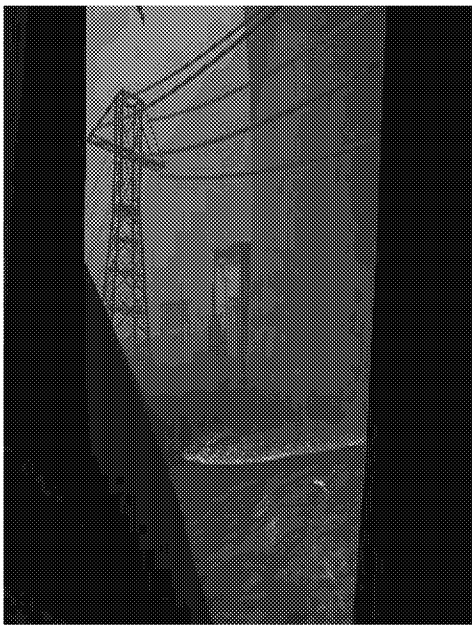
Hazard

The inherent toxicity of a compound. Hazard identification of a given substance is an informed judgment based on verifiable toxicity data from animal models or human studies.

(EPA's Glossary of Terms of the Environment)



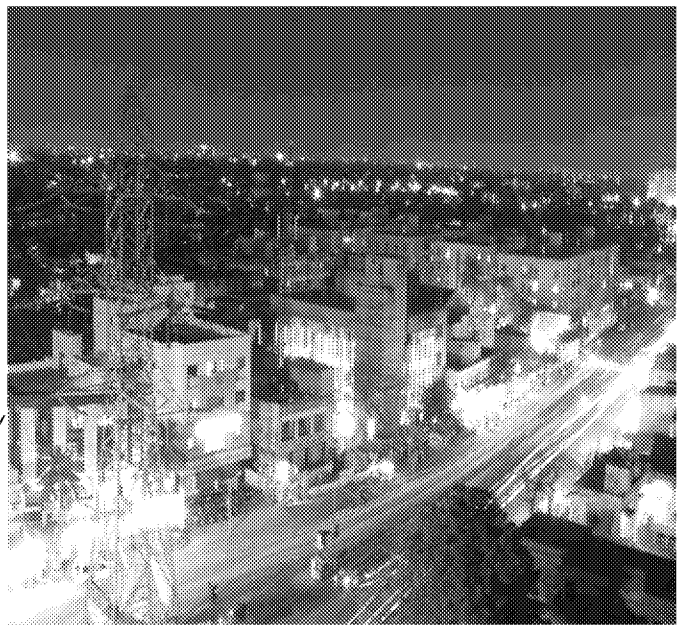
There are multiple definitions for hazard, but in general, hazard addresses the question, "what kind of harm are you dealing with?"
Hazard identification determines the nature of effects produced by an agent. Does the agent or chemical cause cancer or reproductive changes?
Hazard / agent / stressor may be used synonymously. Human health risk assessors usually prefer hazard or agent depending on the specifics of the risk assessment.
Some definitions consider "hazard" to be the description of the harm caused. For example the toxicity value associated with a particular compound.

Another example of inherent property:
Inherent property of an agent or situation having the potential to cause adverse effects when an organism, system or (sub)population is exposed to that agent. [International Programme on Chemical Safety (IPCS) / Organisation for Economic Co-operation and Development (OECD), 2004]
This last example definition brings in the concept that an exposure is required for harm to happen.

Exposure

Quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut).

From EPA's IRIS Glossary



Exposure answers the question "how much of a substance is an individual (or population) exposed to?"

Contact is required for exposure, and without exposure, there is no dose.

Contact is made between the chemical, physical, or biological agent and the outer boundary of the organism. Examples of the outer boundary of an organism might be the skin, lungs, or gut.

A concentration of a substance or chemical in the environment doesn't become a dose until exposure occurs.

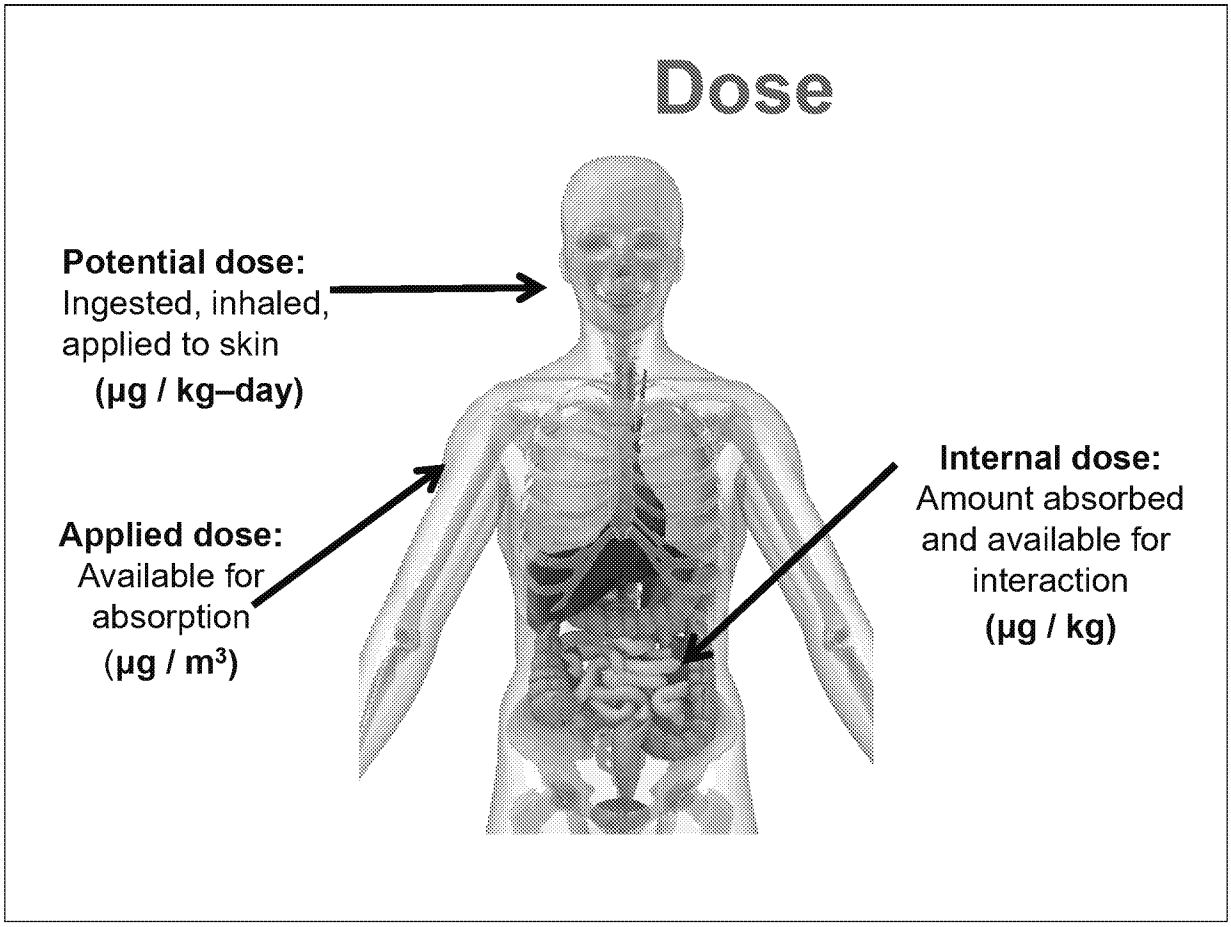
Exposure Assessment

- Identifying the pathways by which toxicants may reach individuals, estimating how much of a chemical an individual is likely to be exposed to, and estimating the number likely to be exposed (EPA's Terms of Environment).
- The determination or estimation (qualitative or quantitative) of the magnitude, frequency, or duration, and route of exposure (EPA's Exposure Factors Handbook).

An exposure assessment is the process of estimating the magnitude (dose), frequency (daily, or event based), and duration (how long) of human (or animal) exposure to a substance.

An exposure assessment considers the:
Exposure pathway – The physical course (e.g., through the air or water) that a chemical takes from its emission by the facility to the exposed individual and is related to the type of release (how the chemical enters the environment)
Exposure route - The way a chemical enters an organism after contact (e.g., by ingestion, inhalation, dermal absorption).
Exposure media - Material (e.g., air, water, soil, food, consumer products) surrounding or containing an agent.
Media is captured in pathway.
Exposure source - An entity or action that releases a stressor to the environment (or imposes a stressor on the environment).
Origin of an agent.

The size and often the characteristics (e.g., age, pre-existing disease) of the population are also considered..



A definition for dose is included in many different EPA documents:
Exposure Factors Handbook
Glossary of IRIS Terms
Guidelines for Carcinogen Risk Assessment 2005
Air Toxics Risk Assessment Reference Library

Definition from the EPA's IRIS glossary: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism.
Dose answers the question: How much chemical has the individual been exposed to? (Dose is a function of exposure concentration and time)
The concept of dose becomes somewhat easier to define if specific modifiers are added.
For example, the following terms are defined in EPA's Guidelines for Exposure Assessment:
Applied dose is the amount at an absorption barrier (like the skin, lungs, GI tract) and available for absorption. This dose has not necessarily crossed the outer boundary of the organism. The units are often µg/m3. (Arrow points to air beside figure.)
Potential dose is the amount of chemical ingested, inhaled, or in a material applied to the skin. It's the potential amount of the chemical that could be absorbed if the chemical were 100% bioavailable. This amount is analogous to the administered dose in a dose-response experiment. (Arrow points to facefigure.)
Internal dose is the amount of a chemical that has been absorbed and is available for interaction with biologically significant receptors. (Arrow points to lungs.)

Dose-Response Assessment

- Evaluating the quantitative relationship between dose and toxicological responses. (EPA's Terms of the Environment)
- A determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response.

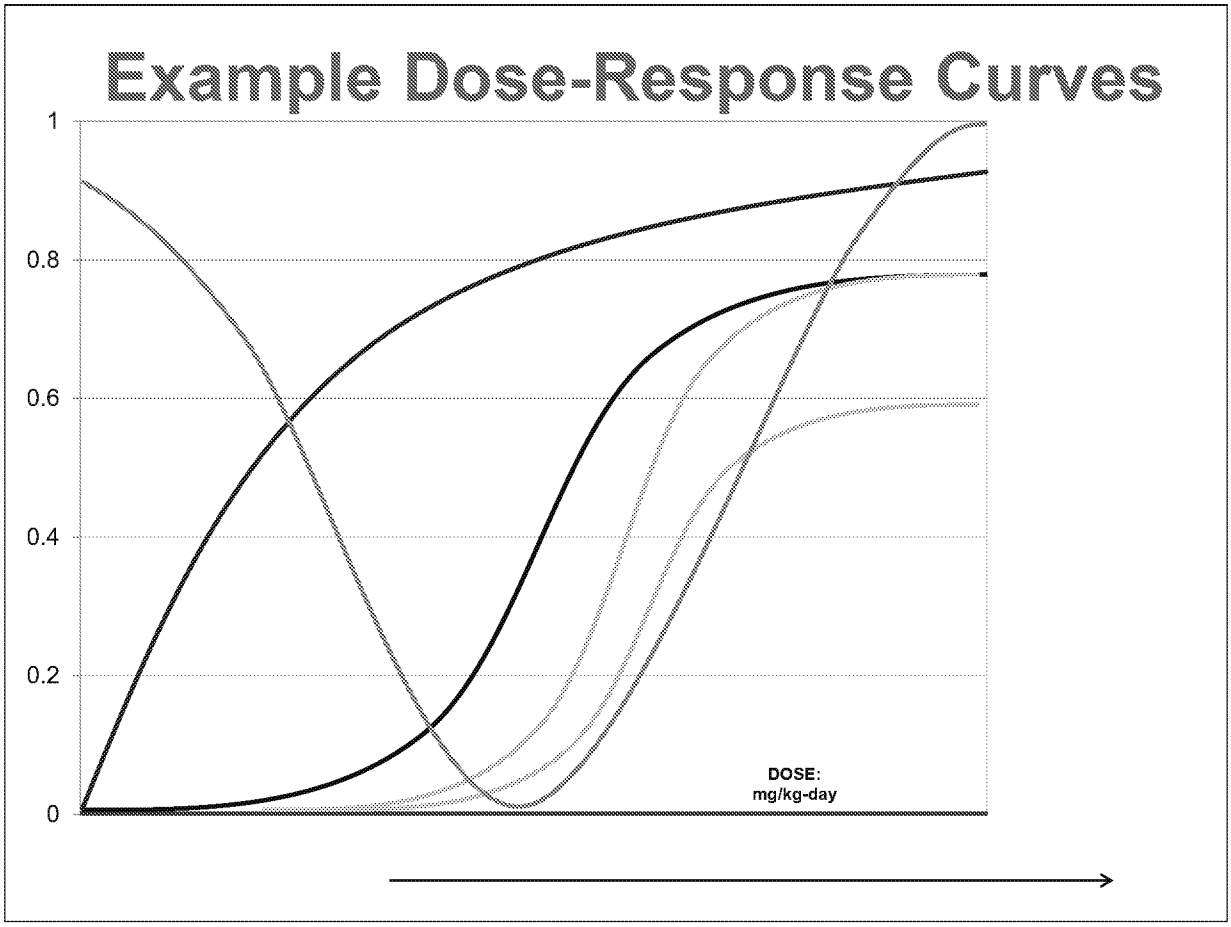
  Response can be expressed as:
  - Measured or observed incidence or change in level of response
  - Percent response in a group of subjects (or populations)
  - Probability of occurrence or change in level of response within a population. (EPA's IRIS Glossary)

Dose-response assessment is sometimes called "Toxicity Assessment." A dose-response assessment evaluates the relationship between the dose (or amount) of a chemical and the corresponding effects. A dose-response assessment attempts to answer the question, "how much or a chemical can an individual be exposed to without seeing effects" or in other words "what is a generally safe dose?"

Dose-response assessments are the primary piece of the risk assessment paradigm.

A key concept in dose-response is that it is a relationship between the dose and the effect seen or expected to occur in animals or humans. This is the basic idea that health responses are not simply yes or no, but there is a continuum of responses.

Note that the term response captures a lot of different ways to look at response:
Measured or observed incidence or change in level of a response (can be a continuous measure or a snapshot in time)
Change in level or type of response (may be symptom or level of severity)
Population based: A percent response in a group of subjects (or populations)
Probability-based: Probability of occurrence or change in the level of response within a population.



Dose-response assessment is quantitative. Here is an example dose-response curve showing the fraction of people who are likely to exhibit a given effect at varying doses.
Note that, as you would expect:
at doses close to zero, very few people will be affected
at very high doses, most of the population will exhibit an effect
<animate> For a chemical that is less toxic than the one represented in this plot, the dose-response curve would be shifted over to the right. <animate> And for a chemical more toxic, the dose-response curve would be shifted to the left--indicating that lower doses, more responses are observed.

The slope and shape of the curve may vary greatly depending on the specific chemical and effect being analyzed.

Not all dose-response curve are sigmoidal (or s-shaped). For example, <animate>, this is a u-shaped dose response curve. Can you think of a type of chemical that may exhibit a dose-response relationship similar to this shape? Substances that are required for normal physiologic function and survival (e.g., vitamins and essential trace elements such as zinc, iron, selenium, etc.). So at a very low dose, there is a high level of adverse effect, which decreases with an increasing dose. As the dose is increases to a point where the deficiency no longer exists, no adverse response is detected; however, if the dose increased abnormally high, an adverse response may occur.

<animate> The red curve is a typical dose-response curve that may be observed for carcinogenic effects.

So remember that the shape of the dose-response curve will vary depending on the chemical to which the individual or population is exposed, as well as the responses (or effects) being measured.

Risk Characterization

- The last phase of the risk assessment process that estimates the potential for adverse health or ecological effects to occur from exposure to a stressor and evaluates the uncertainty involved.

  (EPA's Terms of Environment)

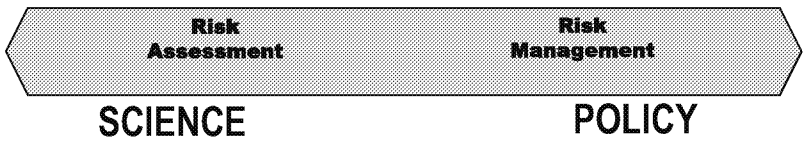
- The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people.

  (EPA's IRIS Glossary)

Finally, risk characterization integrates the hazard identification, exposure assessment, and dose-response assessment components to estimate the potential for adverse health or ecological effects resulting from exposure.

Uncertainty analysis is also incorporated in the risk characterization component of the risk assessment paradigm. Our uncertainty depends on the data we used in the previous four components of the process. For example, if we used dose-response data for mice and extrapolated those results to humans, our uncertainty will be higher than if we were basing our dose-response assessment on epidemiological or clinical study data. Our uncertainty might be expressed and applied as a number, for example, an uncertainty factor, but it will also be described qualitatively.

Risk Assessment and Risk Management Are Interrelated



- Risk assessors and risk managers need to have a good sense of when a decision is scientific judgment versus when it is a policy decision informed by science.
- Opinions vary on how separated risk assessment and risk management should be.
- The most current frameworks recommend an iterative process.
- Transparency is key.

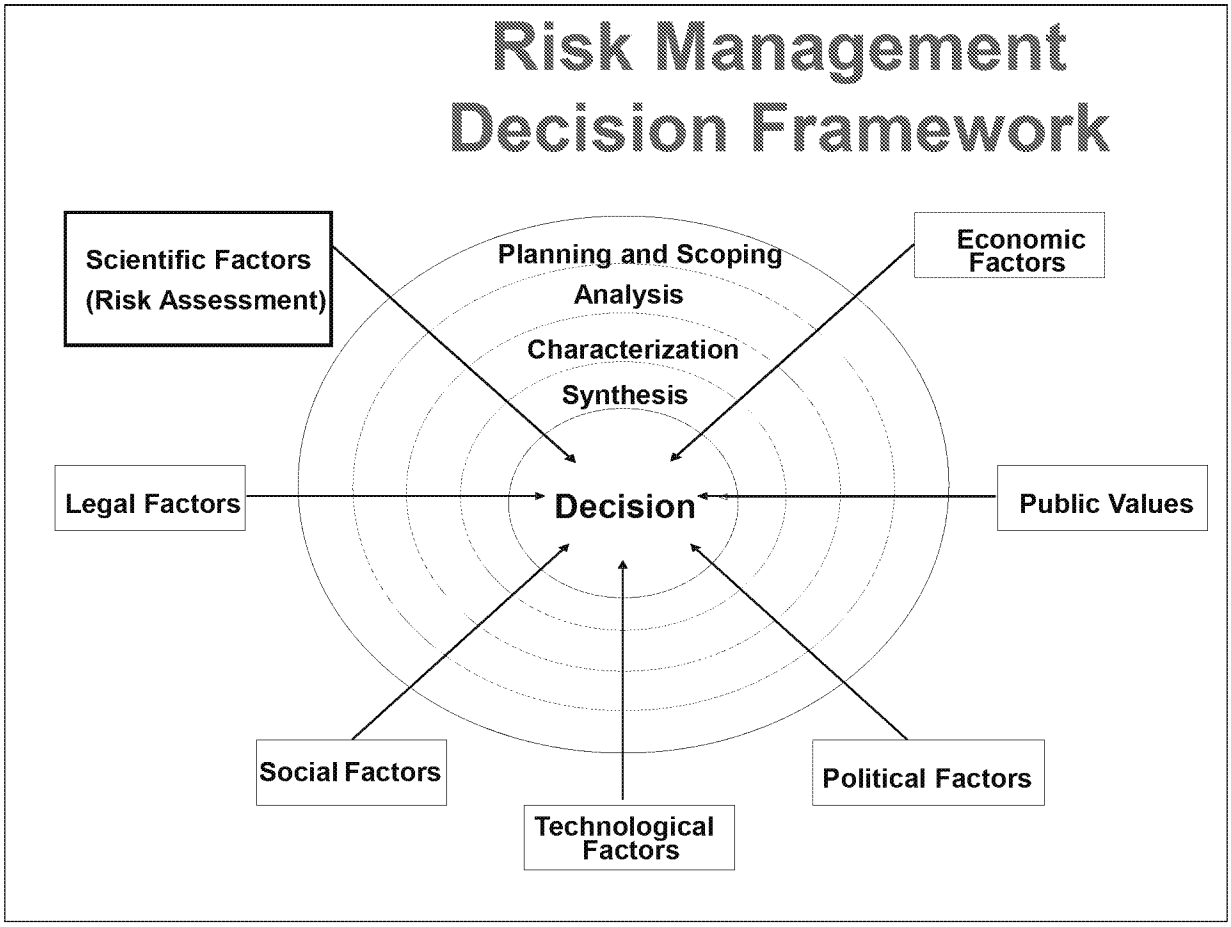
Risk assessment and risk management are two components of the risk analysis paradigm introduced earlier (along with risk communication). Recall that the circles for each of these overlap.

In conducting a risk assessment and using the results to make a risk-based decision, there is typically a continuum of decisions ranging from those that are clearly scientific judgment to those that are clearly policy decision. But then there are some decisions that are made during risk assessment that fall in the grey zone. In these cases it may be uncomfortable for either risk managers or risk assessors to claim the decision.

Early on risk assessment and risk management were so interwoven the process lacked transparency. There was a push to separate risk managment from risk assessment was so that these 2 types of decisions would not be confused. So the separation of risk assessment and risk management became very deliberate and as complete as possible.

The current trend, however, is to recognize that the process is iterative, so risk managers and risk assessors communicate and work together but there is also transparency regarding what aspects of the decision and process are risk managements and what aspects are risk assessment.

Risk assessment is a non-linear process, and it may be also an iterative process. This involves a dialog between risk assessors and risk managers about the scope of the risk assessment.
Risk assessors and risk managers work together to develop the questions the risk assessment will address.
The iterative process can also include screening level risk assessments that can help pare down the scope of a detailed quantitative risk assessment.
Successive iterations of RA can incorporate new information on risk management options and risk mitigation approaches.
Finally, transparency is conducting a risk assessment in such a manner that all of the scientific analyses, uncertainties, assumptions, and science policies which underlie the decisions made throughout the risk assessment are clearly stated (i.e., made readily apparent).



Risk managers use many components in their in preparing their risk management decision. Risk assessment is only one component. Risk managers usually consider economic factors, public values, political, technological, social and legal factors to render their decisions.

Risk Assessment Steps in Details

Risk managers use many components in their in preparing their risk management decision. Risk assessment is only one component. Risk managers usually consider economic factors, public values, political, technological, social and legal factors to render their decisions.

Planning and Scoping

Identify the Problem

- Where does the problem exist?
- Who or what is affected?
- What causal agents should be considered?
- What are the system boundaries?
- What are risk management needs?
- What are stakeholder needs?

The first step in risk assessment process, is to identify the problem.

What do risk assessors mean by "identify the problem?"

An important goal at this stage is to identify where the problem exists, who or what is affected, what causal agents will be considered, and what the systems boundaries will be. In addition, it is necessary to identify risk management needs and to consider the needs of stakeholders involved.

EPA definition of problem formulation: The initial process for scoping the problems, Decision Contexts, and Partner/Stakeholder needs necessary for developing the Research Framework, Research Action Plan, and Research Program Strategic Plan. [EPA Path Forward Glossary]

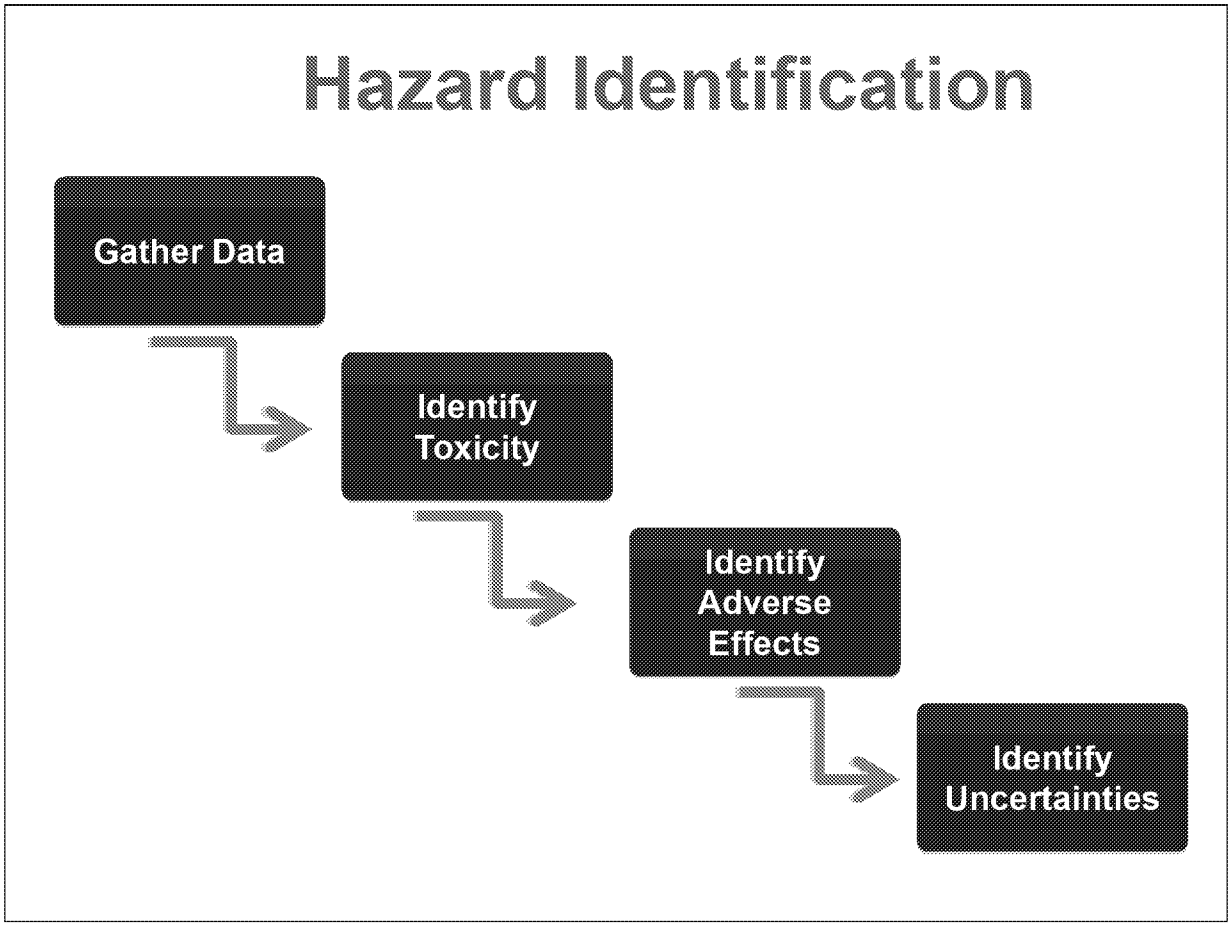
HAZARD IDENTIFICATION

Following planning and scoping, we conduct hazard identification

Hazard Identification

- Process of determining if exposure to a chemical agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defects) and if the adverse health effect is likely to occur in humans

Hazard Identification: Process of determining if exposure to a chemical agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defects) and if the adverse health effect is likely to occur in humans



We can divide the hazard identification process into 4 main components.

1) We must gather the data about the chemicals of concern. If we are doing a site-specific risk assessment, we gather data about chemical concentrations at the site.

2) Then determine how toxic is the chemical?

3) We have to identify the adverse effects caused by the chemical.

4) And we must determine what uncertainties are associated with the data or the effects.

Let's talk more about these four components of hazard identification.

Gather Data

What are the chemicals?
Which populations might be affected?
What toxicity data are available?
Human Data
Epidemiology studies
Controlled human exposure studies
Animal Bioassay Data
Other Data
In Vitro Data
Structure-activity relationships
Metabolic data
Genomics

After identifying the chemicals of concern, we need to gather data to answer the question "How toxic is this chemical?" In other words, does the chemical cause cancer or noncancer adverse effects in humans and at what dose? We should remember the quote, "The dose makes the poison."

Does anyone know who this quote is attributed to?
Paracelsus – 16th century Swiss physician/chemist

We must first identify the chemical and then learn about its chemical and physical properties.

We need to think about which populations might be affected by the chemical and specifically, which populations might be more sensitive or susceptible (e.g., children, asthmatics).

We gather in vivo ("within the living") data including:
Human data
Epidemiology studies
Controlled human exposure studies
Animal data
The animal studies might be chronic, subchronic, acute, or developmental and reproductive studies.

And we compile other data. We might use in vitro ("within the glass") data, data on structure-activity relationships, metabolics, or genomics.

A key question that risk assessors debate is whether these data must be available on the chemical of interest or whether inference can be drawn from "related" compounds for which data are available

Identify Toxicity

- Effects – What effects are observed from the data collected?
- Toxicokinetics – What does the body do to the chemical?
- Toxicodynamics – What does the chemical do to the body?
- Mode of action – How does the chemical act to produce an effect?
- Weight of evidence – How likely is this chemical to cause non-cancer effects or cancer and under what conditions?
- Causality Framework – A way to organize and evaluate toxicity information to assess causality given those data.

Identify Types of Effects

What are the adverse effects?

- What are the affected organs or tissue systems?
- What is the severity of effects?
- Who is more sensitive or susceptible?
- What factors affect susceptibility?

Types of Effects

- Adaptive
- Compensatory
- Adverse
- Critical
- Frank

After gathering the data and reviewing it, we next determine the adverse effect.

We need to know which organ or tissue systems are affected by the chemical.

What is the severity of the effect? Not all effects are the same, so we can compare them more easily by distinguishing between the severity of the effects.

Probably the least severe, an adaptive effect enhances an organism's performance or its ability to stand up to a challenge.

A compensatory effect means the body maintains its function without enhancement or any significant cost.

A critical effect is the first adverse effect that occurs as the dose rate or exposure level increases. One or more effects may be critical. The critical effect might also be the first known precursor of the adverse effect.

An adverse effect is a biochemical change, functional impairment, or pathologic lesion that affects the performance of the whole organism, or reduces an organism's ability to respond to an additional environmental challenge.

A frank effect is an unmistakable adverse effect, such as convulsions or mortality. It is an irreversible adverse effect.

(The above definitions are from Table C-1 in U.S. EPA. (2007) Concepts, Methods and Data Sources for Cumulative Health Risk Assessment of Multiple Chemicals, Exposures and Effects: A Resource Document. U.S. Environmental Protection Agency, National Center for Environmental Assessment, Cincinnati, OH. EPA/600/R-06/013F.)

After identifying the effects of the chemical and the severity of those effects, we also consider who might be more sensitive or susceptible to the chemical. We ask, do certain characteristics make people more sensitive or susceptible to these effects?

People who are "sensitive" experience a greater response at the same internal dose due to some intrinsic and possibly unknown factors.

"Susceptible populations" have an increased probability of experiencing health effects following exposure. The increased probability results from genetic or developmental factors, race, gender, age, lifestyle (like smoking status and nutrition), or preexisting diseases. At the population level, socioeconomic status, including access to health care and education level might impact susceptibility.

- Which populations might be more susceptible to lead poisoning? Young children since lead affects neurocognitive development.

- Which populations might be more sensitive to carbon monoxide? People with heart or lung conditions are most sensitive.

Identify Uncertainties

What introduces uncertainties?

- Human variability
- Using animal data
- Extrapolating the study duration
- Extrapolating the exposure effect level
- Relevance to target context (human exposures)
- Strength of database
- Quality of data

In the hazard identification component of the risk assessment, we also need to examine the uncertainties. Many parts in the hazard identification could introduce uncertainties. These are some examples:

Human Variability: inherent differences from one human to another make individuals respond differently to the same hazard. One way we account for human variability is to apply ADAFs or age-dependent adjustment factors.

Uncertainties can arise when we have animal data and we extrapolate to apply it to humans.

We get uncertainties when we take data from a subchronic study and extrapolate it to a chronic exposure.

We also get uncertainty when we extrapolate from a lowest-observed-adverse-effect level (LOAEL) to a no-observed-adverse-effect level (NOAEL).

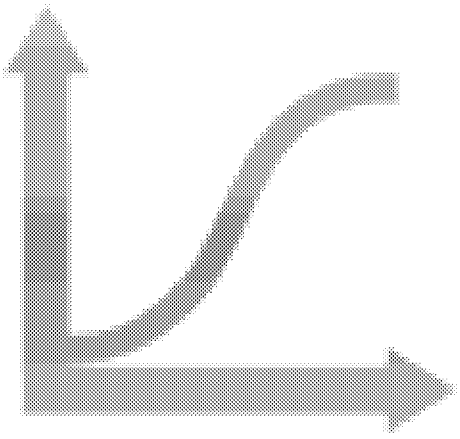
We consider the relevance of the data to the target context – whether the data we have is for the same kind of exposure. If we are using data obtained from inhalation studies to apply to ingestion exposure, we have to consider this additional uncertainty.

Finally, we have to consider the database we are using. The strength of the database and the quality of the data must be considered.

If we have ideal data, we will have minimum uncertainty. Fluorine (soluble fluoride) is an example. There are lots of human epidemiologic studies with a large total population that has been studied over an extensive period of time.

An example of a chemical with more uncertainty is acetone. Uncertainties arise for acetone from extrapolating from animal data to apply to humans, extrapolating data from a subchronic study to chronic exposure, and the strength of the database.

DOSE-RESPONSE ASSESSMENT



The next few slides will focus on DOSE-RESPONSE ASSESSMENT

Dose-Response Assessment

- **Dose-Response Assessment** – a determination of the relationship between the magnitude of an administered, applied, or internal dose and a specific biological response. Responses can be expressed as:
  - Measured or observed incidence or change in level of response
  - Percent response in groups of subjects (or population), or
  - The probability of occurrence or change in level of response within a population
- **Dose-Response Relationship** – the relationship between a quantified exposure (dose) and the proportion of subjects demonstrating specific biologically significant changes in incidence and/or in degree of change (response).

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Dose-Response Relationship – the relationship between a quantified exposure (dose) and the proportion of subjects demonstrating specific biologically significant changes in incidence and/or in degree of change (response).

Dose-Response Terminology

Characterize Dose-Response Relationship
Identify a **NOAEL** or **LOAEL**
Conduct dose-response modeling and **BMD Modeling**

LOAEL
Lowest-Observed-Adverse-Effect Level. Lowest dose at which significant effects are observed.

NOAEL
No-Observed-Adverse-Effect Level. Highest dose at which no significant adverse effects are observed.

LED_{10}
Dose that produces an adverse effect in 10% of exposed, relative to control.

BMD
Benchmark Dose. An exposure to a low dose of a substance that is linked with a low (1-10%) risk of adverse health effects, or the dose associated with a specific biological effect.

BMDL
A lower, one-sided confidence limit on the BMD.

Some of the basic terms used to describe specific points in the process of dose-response assessment are presented on this slide.

(sources: EPA Benchmark Dose (BMD) Methodology Page - http://www.epa.gov/ncea/bmds/bmds_training/methodology/intro.htm#BMD , EPA IRIS Glossary Page - http://www.epa.gov/iris/gloss8_arch.htm#n)

LOAEL, NOAEL, LED10, and BMDL doses are used in the process of risk assessment as points of departure for decision-making purposes.

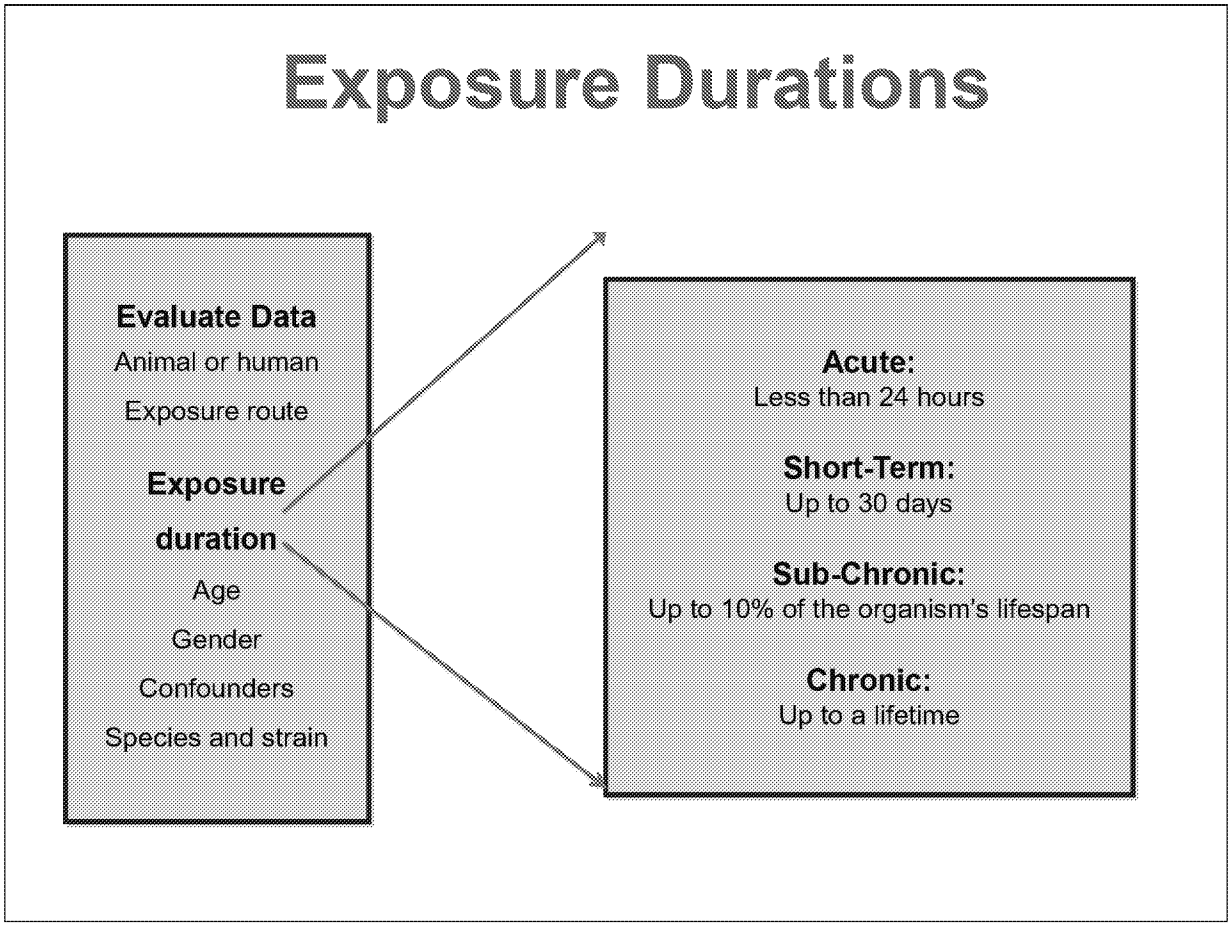
The LOAEL is the lowest dose at which a biologically or statistically significant increase in the frequency or severity of an adverse effect is observed in the exposed population. The increase is compared to the control population to determine whether a significant difference exists.

The NOAEL is similar to the LOAEL, but it represents the level at which there are no biologically or statistically significant increases in the frequency or severity of adverse effects compared to the control population. There may be effects observed at the NOAEL, but they are not determined to be adverse or precursors to adverse effects. If several NOAELs are observed in a study, the regulatory focus should be on the highest NOAEL.

The LED10 is the 95% lower confidence limit of the dose of a chemical needed to produce an adverse effect in 10 percent of those exposed to the chemical, relative to the control. This type of value is used as a point of departure for substances for which any dose above zero might potentially result in an adverse effect or a precursor to adverse effect.

The BMD (or BMC for inhaled substances) is a dose associated with a specific, low incidence of risk (usually in the range of 1-10%) of a health effect. The BMD can also be associated with a specific measure or change of a biological effect as determined by the investigators. The BMDL is the lower confidence limit on the BMD which will result in the required response, as identified by the investigators.

BMD may also refer to the approach of benchmark dose modeling, and can be contrasted with the approach that uses LOAEL/NOAEL by its use of extrapolation from a calculated point of departure rather than an experimental dose.

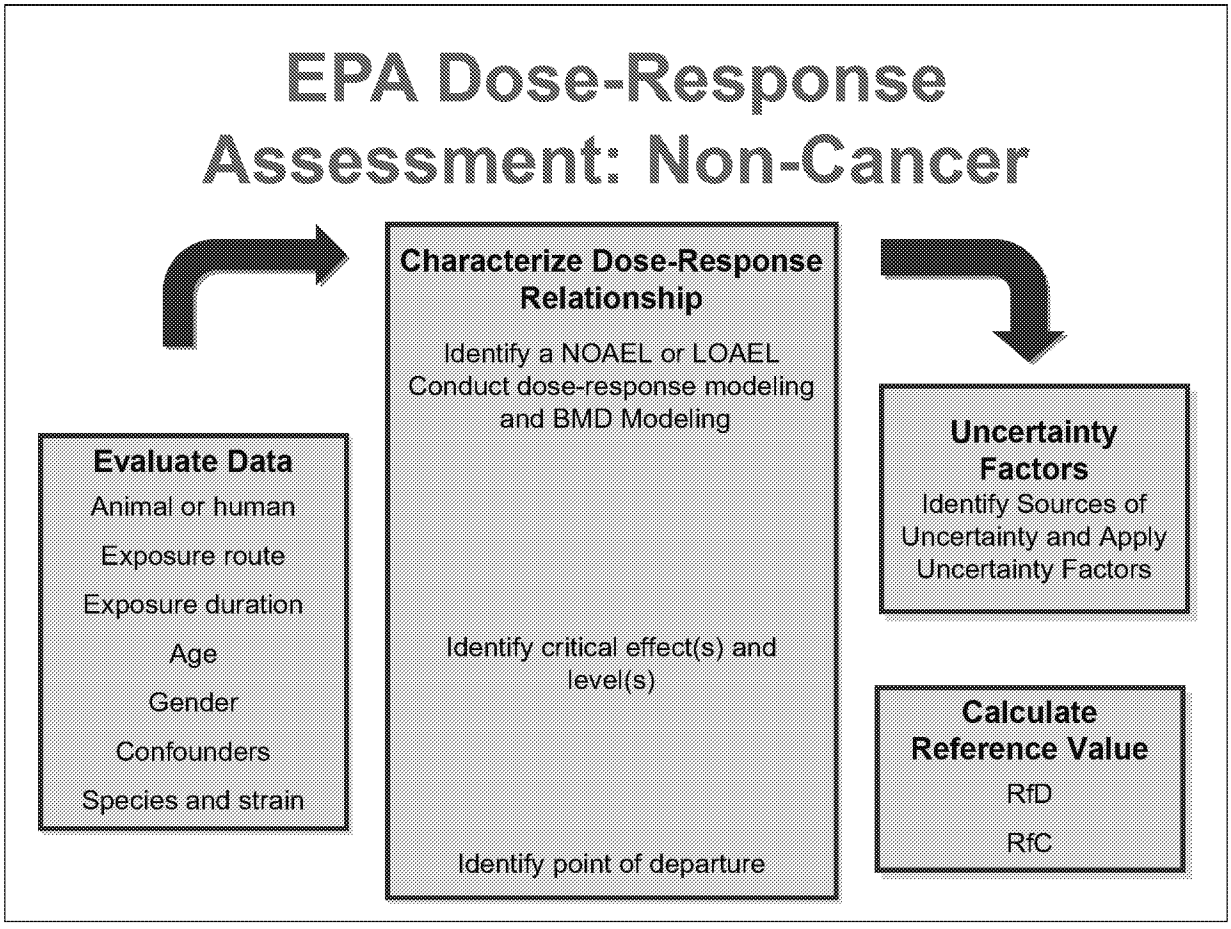


Acute Exposure Definition: Exposure by the oral, dermal, or inhalation route for 24 hours or less.

Short Term Exposure Definition: Repeated exposure by the oral, dermal, or inhalation route for more than 24 hours, up to 30 days.

Longer-Term (Subchronic) Exposure Definition (: Repeated exposure by the oral, dermal, or inhalation route for more than 30 days, up to approximately 10% of the life span in humans (more than 30 days up to approximately 90 days in typically used laboratory animal species).

Chronic Exposure Definition: Repeated exposure by the oral, dermal, or inhalation route for more than approximately 10% of the life span in humans (more than approximately 90 days to 2 years in typically used laboratory animal species).



This overview is a simplification of the process, but is useful for understanding the dose-response assessment process as a whole.
For dose-response assessment, we begin by considering the data we obtained during the hazard identification phase. We examine the available animal and human data.
What are the exposure routes we would examine?
Inhalation
Ingestion (oral gavage, by mouth)
Dermal
Transdermal
Injection
Subcutaneous
Intramuscular
Intravenous
Intraperitoneal (injection directly into intestines)
Tail vein

We examine the data from all available exposure routes.

We consider what we know about the population. Do we have data for different ages, genders? Do we have data for populations that might be either more susceptible or more sensitive?

What confounders are associated with the data?

If we are using animal data, we need to know the species and strain of animals tested.

Then we characterize the dose-response relationship.

We identify the point in the dose-response data where there is no observed adverse effect (the NOAEL) or the lowest dose

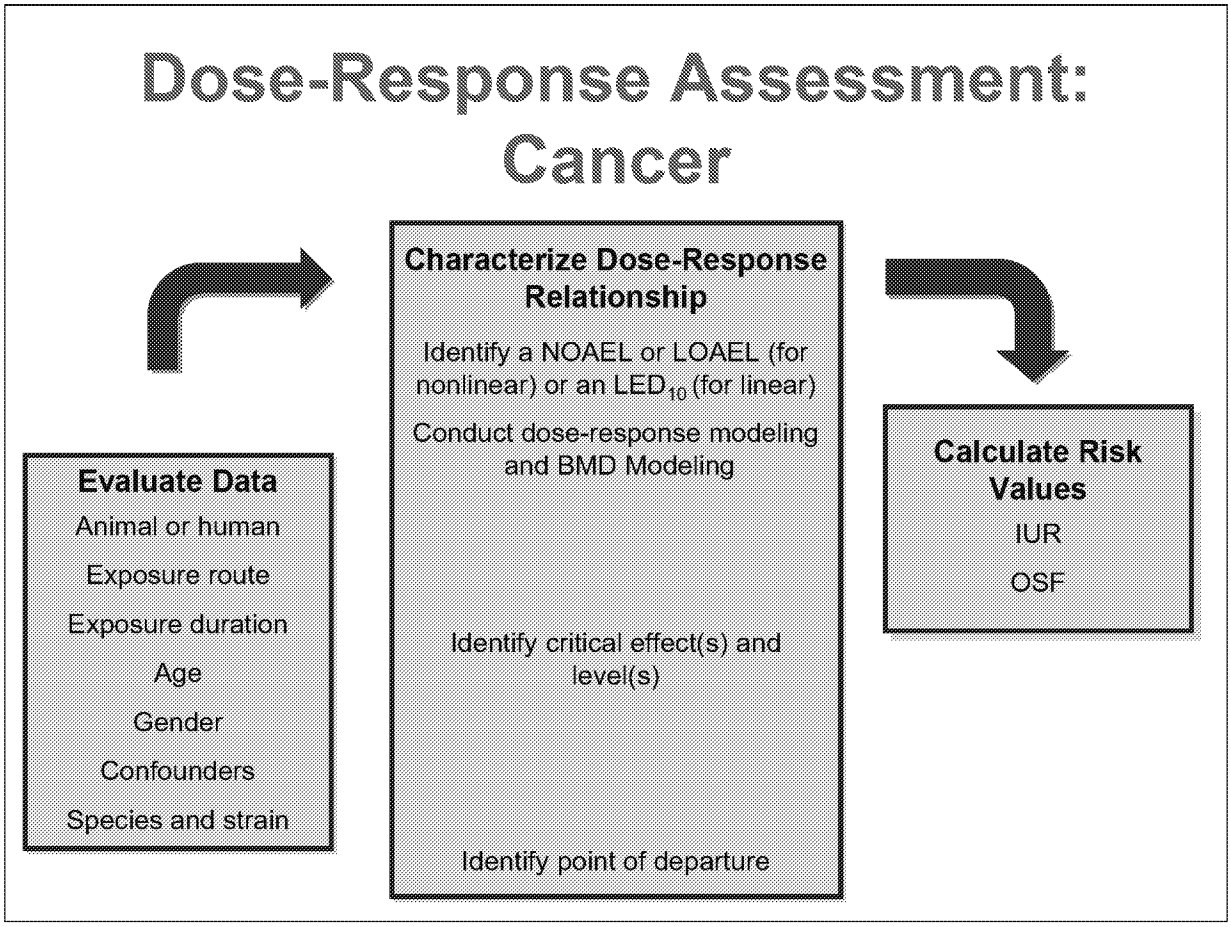
associated with an observed adverse effect (the LOAEL). Sometimes we need to do dose-response modeling (like benchmark dose modeling). We identify from the data the critical effect – the first adverse effect to occur - and the level where it occurs. Finally, from this data, we identify the point of departure. It is the starting point of the dose-response curve for the critical effect from which we eventually estimate the human health reference value.

We apply uncertainty factors to reflect the limitations of the data we use.

The application of uncertainty factors is discussed in guidance documents such as EPA's "Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry" (1994).

The result of these steps is a reference value. It is an estimate of human exposure, for a specific duration and route that is likely to be without an appreciable risk of adverse health effects over a lifetime. It might be a reference dose for ingestion exposure (RfD) or a reference concentration (or RfC) for inhalation exposure.

The dose-response assessment is captured in the process of developing an IRIS assessment. It is important to remember that an IRIS value is the result of a dose-response assessment, but not necessarily the result of the entire risk assessment process in the strictest sense of the definition.



Just as with the non-cancer dose-response assessment, this diagram of the cancer dose-response assessment is simplified, but provides a general overview of the process.

The dose-response process for cancer endpoints is similar to that for non-cancer endpoints, but there are distinct differences.

For example, the mode of action of the substance is evaluated to determine whether the dose-response relationship at low doses is expected to be nonlinear (like most noncancer effects) or linear (the default for cancer).
It is important to note that this evaluation will affect which type of value the point of departure is based on.

Another major difference between non-cancer and cancer dose-response assessments is that risk values rather than reference values are derived for carcinogens. Risk values include the inhalation unit risk (IUR) and oral slope factor (OSF).

The IUR represents the upper-bound excess lifetime cancer risk that is estimated to result from continuous exposure to an agent at a concentration of 1 microgram per liter of water or 1 microgram per cubic meter of air.

The oral cancer slope factor (OSF) is an upper bound, at approximately the 95% confidence limit, of the increased cancer risk from lifetime exposure to an agent, and is written in units of milligrams per kilogram per day.

Reference Values

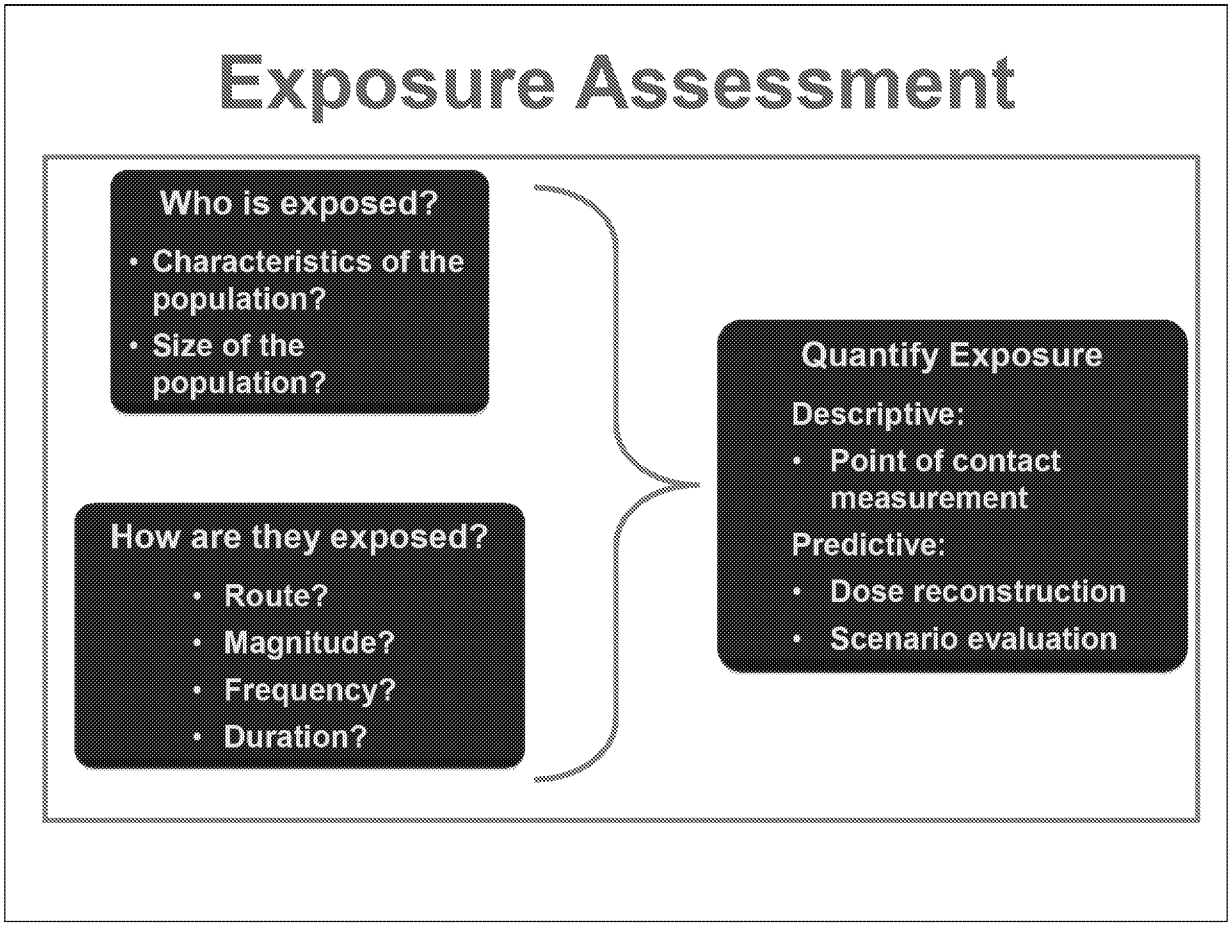
- Reference values are developed over a range of exposure contexts (e.g. duration, scenario….):
  - Worker- or general public-exposures in emergency response situations (usually acute or short-term)
  - Worker-exposure in occupational settings (workday/week)
  - Continuous, lifetime (or some other long-term) exposures to the general public (e.g. chronic)
- So it is important to understand the purpose and appropriate application of the reference value

It is important to remember that reference values are contextual, and developed over a range of exposure contexts (e.g. duration, scenario....):
For example:
Worker- or general public-exposures in emergency response situations are usually acute or short-term
Worker-exposure in occupational settings may be represented by the workday work-week, or work-year
Lastly, an important category for developing reference values comes from continuous or lifetime (or some other long-term) exposures to the general public (e.g. chronic)
So it is important to understand the purpose and appropriate application of the reference value

EXPOSURE ASSESSMENT

Now we will discuss exposure assessment

EXPOSURE ASSESSMENT



Exposure Assessment Definition: An identification and evaluation of the human population exposed to a toxic agent, describing its composition and size, as well as the type, magnitude, frequency, route and duration of exposure. In practice, exposure assessment is the process of measuring or estimating the magnitude, frequency, and duration of human exposure to an agent in the environment or estimating future exposures for an agent that has not yet been released.

Who is exposed?

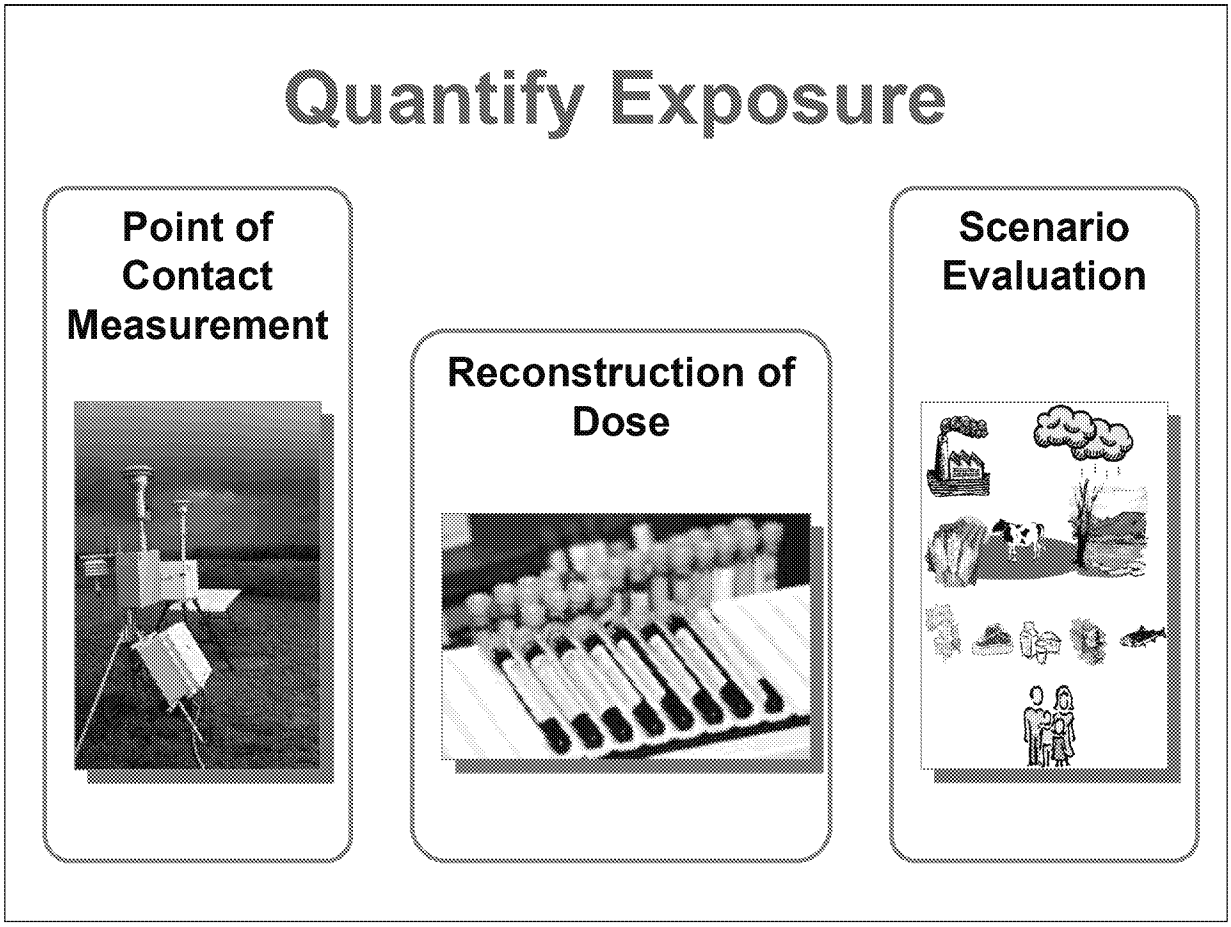
We need to know characteristics of the population including the timing of their exposure. For example, does the exposure occur when they are developing?

How are they exposed?

What are the possible routes of exposure?
We need to know the route, magnitude, frequency, and duration.

From this information we work to quantify exposure. We might do point of contact measurement, scenario evaluations, or reconstruction of dose.

Let's talk more about how exposure is quantified.



Typically we quantify exposure in one of three ways:

A point of contact measurement

We might take measurements of the concentration of a chemical over time at or close to the point of contact between the chemical and the person while the exposure is taking place. This is a point-of-contact measurement of exposure.

Examples of a point of contact measurements are:
- Radiation dosimeter that an individual wears
- Personal air sampler

2) Reconstruction of the Dose

Sometimes we reconstruct the dose. This is a way to quantify an internal dose, so it's done by taking measurements from the body – evidence that exposure has occurred. We measure internal body indicator. such as body burden or biomarkers:
- Concentration of chemical in tissue, blood, urine, breath, hair, etc.
- Concentration of chemical's metabolites (for example, cotinine is a metabolite of nicotine, which is a component of tobacco products as well as environmental tobacco smoke. It is possible to detect Cotinine in the blood as a biomarker of exposure of tobacco products and environmental tobacco smoke. (U.S. EPA, 2010))

3) And sometimes we do scenario evaluation. We measure or estimate the amount of a substance contacted and the frequency and duration of contact. We use equations and assumptions to mathematically calculate/estimate dose.

Exposure Assessment Equations

$$\text{Exposure Concentration}\left(\frac{\mu g}{m^3}\right) = \frac{\text{Concentration}\left(\frac{\mu g}{m^3}\right) \times \text{Exposure Time}\left(\frac{hours}{day}\right) \times \text{Exposure Frequency}\left(\frac{days}{year}\right) \times \text{Exposure Duration}\,(years) \times \text{Conversion Factor}\left(\frac{year}{8{,}760\ hr}\right)}{\text{Averaging Time}\,(years)}$$

$$\text{Potential Dose}\left(\frac{mg}{kg-day}\right) = \frac{\text{Concentration}\left(\frac{mg}{kg}\right) \times \text{Intake Rate}\left(\frac{mg}{day}\right) \times \text{Exposure Duration}\,(days) \times \text{Conversion Factor}\left(\frac{kg}{10^6\ mg}\right)}{\text{Averaging Time}\,(days) \times \text{Body Weight}\,(kg)}$$

$$\text{Absorbed Dose}\left(\frac{mg}{kg-day}\right) = \text{Potential Dose}\left(\frac{mg}{kg-day}\right) \times \text{Absorption Fraction}$$

Let's talk more about the equations we would use for an exposure assessment, mainly those we would use to estimate exposure when we do scenario evaluation.

Exposure is concentration integrated over time. The area under the curve is the magnitude of the exposure. This definition comes from EPA's 1992 Guidelines for Exposure Assessment. The equation is a helpful way to think about long-term inhalation exposure.
Alternately, since we do not usually have concentration measured continuously over the exposure duration, we estimate the inhalation dose.

We calculate inhalation exposure concentration by multiplying the concentration in air by the exposure time, frequency, and duration and dividing by the averaging time.
Method for calculating potential dose:

Often though, we also want to calculate a long-term or a short-term dose in units of chemical mass per body weight per time.

We calculate this potential dose via the oral route by multiplying concentration by intake rate and exposure duration and dividing by averaging time multiplied by body weight. The units should be mg/kg-day.

For dermal exposures we get an absorbed dose by multiplying the potential dose by the absorption fraction (AF). The absorption fraction is the ratio of how much mass is absorbed over how much mass was applied, so it is dimensionless. The absorption fraction will depend on the route of exposure and the characteristics of the chemical(s) in question. For instance, the absorption fraction for dermal exposure will depend on the tendency of the chemical to cross the skin, as well as the way that the person is exposed. Dermal exposure to liquids (i.e., water) containing the chemical is likely to be much different than exposure to solids that the chemical has adsorbed to (i.e., soil). The absorption fraction for cadmium has been published by the U.S. EPA in the Risk Assessment Guidance for Superfund Volume 1 (Exhibit 3-4, page 3-16), and has a unitless value of 0.001.

What references can we consult to get values for exposure factors?
- Exposure Factors Handbook and Child-Specific Exposure Factors Handbook.

- Superfund Risk Assessment Guidance or RAGS.

RISK CHARACTERIZATION

Risk Characterization Definition: The integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people

Risk Characterization

Risk characterization is the integration of information on hazard, exposure, and dose-response to provide an estimate of the likelihood that any of the identified adverse effects will occur in exposed people. (IRIS Glossary Definition)

Risk characterization requires:

- Transparency
- Clarity
- Consistency
- Reasonableness

Risk characterization integrates the results of the hazard identification, dose-response assessment, and exposure assessment. Risk characterization is not just a number! However, calculating risk and other numbers and comparing these to appropriate reference points is a major part of risk characterization. For stressors or the chemical identified in the hazard identification, the risk characterization compares toxicity information to the exposure profiles developed for people we think might be exposed.

Risk characterization estimates the likelihood that the adverse effects will occur in people who are exposed. It includes assumptions and uncertainties associated with all steps in the risk assessment process. Major assumptions might include an assumption that exposure lasts for a lifetime. Major uncertainties (e.g., exposure profile may not be representative of real exposures over time because little knowledge of actual exposures). The risk characterization should be transparent. It should disclose the risk assessment methods, default assumptions, rationale, extrapolations, uncertainties, and describe the strength of each step in the assessment.

The final product of the risk assessment should be clear and easily understood by everyone. The risk assessment should be conducted and presented so that it is consistent with EPA policy. The risk assessment should be reasonable, rely on sound judgment, and be consistent with the current state-of-the-science.

Elements of Risk Characterization

- Key Information
- Context
- Sensitive Populations
- Scientific Assumptions
- Policy Choices
- Key Conclusions
- Alternatives Considered
- Variability
- Uncertainty
- Bias and Perspective
- Strengths and Weaknesses
- Confidence Statements
- Research Needs

EPA published the Risk Characterization Handbook in 2002 to help risk assessors in this step of the risk assessment process. The Handbook describes the key elements of risk characterization.

These include:

Key information from all steps of the assessment
Context
Any sensitive or susceptible populations that were identified
Scientific assumptions
Policy choices
Variability
Uncertainty
Bias and perspective
Strengths and weaknesses as well as confidence statements about the studies, chemical database, and the resulting dose-response values
Key conclusions
Alternatives considered
Research needs

Risk Characterization: Outcome

Noncancer Hazard Quotient: Ratio of estimated exposure to reference level at which no adverse health effects are expected.

Noncancer Hazard Index: Summation of the Hazard Quotients for all chemicals to which an individual is exposed

Cancer Risk: Incremental probability of developing cancer for an individual exposed to a given chemical over a lifetime.

(Historically, cancer risks ranging from 1×10^{-4} to 1×10^{-6} are considered acceptable by EPA.)

Risk assessment is an iterative process: The results of risk characterization inform decisions on next steps, including further analysis or risk management actions.

Key risk characterization outcomes in most human health risk assessments include a number. This usually includes a noncancer hazard quotient and/or cancer risk values.

The noncancer hazard quotient is simply the ratio of the estimated exposure to an appropriate non-cancer toxicity reference value. The exact value of the hazard quotient is typically less important than whether an HQ is above or below a certain value, such as one. Note that an HQ of one would suggest that estimated exposures are exactly equal to the toxicity reference value.

It's important to understand that HQs do not scale linearly. For example, an HQ of 4 does not necessarily imply that conditions (or the resulting health impacts) are twice as "bad" as an HQ of 2.

A cancer risk is the incremental probability of an exposed individual developing cancer during their lifetime following exposure to the given chemical, and therefore the value representing the level of risk is very relevant. A cancer risk of 4 in one million could be considered twice as "adverse" as a cancer risk of 2 in one million – that is, the first risk (of 4) is indeed twice a risk of 2.

Historically, cancer risks ranging from 1×10-4 to 1×10-6 (or anything below this range) are considered acceptable by EPA.

Risk Characterization: Quantitative Results

Noncancer Effects

$$\textbf{Hazard Quotient (HQ)} = \frac{\textbf{ADD}\left(\frac{mg}{kg-day}\right)}{\textbf{RfD}\left(\frac{mg}{kg-day}\right)}$$

Cancer

$$\textbf{Cancer Risk (Oral)} = \textbf{LADD}\left(\frac{mg}{kg-day}\right) \times \textbf{Oral Slope Factor}\left(\frac{mg}{kg-day}\right)^{-1}$$

$$\textbf{Cancer Risk (Inhalation)} = \textbf{Lifetime Average Exposure Concentration}\left(\frac{\mu g}{m^3}\right) \times \textbf{Inhalation Unit Risk}\left(\frac{\text{Extra Risk}}{\mu g/m^3}\right)$$

The basic algorithms for calculating hazard quotient and cancer risk are presented here.

For noncancer assessments, we can calculate a hazard quotient by dividing the exposure concentration (or dose) by a reference concentration (RfC) or reference dose (RfD). This is the first equation on our slide here. The HQ we calculate is for a specific exposure duration and chemical. Often, risk assessors say that if the HQ is greater than 1, the exposure might have the potential to cause noncancer health effects. But this is a risk management decision based in part on policy, so sometimes the HQ is compared to a number greater than 1.

For multiple chemicals that affect a target organ, we can sum the HQs we calculate to get a hazard index or an HI.

Often, if the HQ calculated is greater than one, risk assessors review the assumptions used and might conduct a more detailed assessment.

Then we calculate cancer risk a little differently. For cancer, we can calculate the lifetime cancer risk. It is expressed as a probability of the event occurring (1 in a million or 10 in a million or something similar). It is calculated by multiplying exposure by either the cancer slope factor or the unit risk estimate (depending on how we have estimated our exposures – i.e., as a dose or as an average long-term exposure concentration in air or water).

Conclusions

- Risk Assessment is a powerful decision-support tool for a public health regulatory agency
  - Useful when there is not complete knowledge
  - Taking full advantage of information and data by integrating it into a systematic framework
  - Several applications
- Risk analysis encompasses:
  - risk assessment;
  - involves communicating the risk to a broader audience; and
  - ensures that policy considers the public health impact (e.g, decrease in the risk of foodborne illness) of intervention strategies

Conclusions:
Risk Assessment is a powerful decision-support tool for a public health regulatory agency
Risk assessment is useful when there is not complete knowledge
The process of risk assessment is taking full advantage of information and data by integrating it into a systematic framework
Risk assessment has several applications based on the context of risk assessment

Risk analysis encompasses:
risk assessment; involves communicating the risk to a broader audience; and ensures that policy considers the public health impact (e.g, decrease in the risk of foodborne illness) of intervention strategies).

Conclusions (Continue)

Risk assessment is the integration of qualitative and quantitative information on:

- toxicity
- severity of effects
- geographic extent
- exposure
- magnitude of response
- and many other factors

It is an integrated and dynamic process that utilizes scientific estimates to inform environmental and public health risk management decisions.

Risk assessment is not just dose-response assessment alone.

Risk assessment is the integration of toxicity information, exposure profiles, and other qualitative and quantitative information on severity and magnitude of response, geographic extent, and other factors. Risk assessment is not a best scientific estimate of the most likely number of effects that will occur as a result of environmental exposures. It is an integrated and dynamic process that utilizes scientific estimates to inform environmental and public health decision-making.

So in conclusion, risk assessment is not dose-response assessment alone. Dose-response assessment, taken together with exposure assessment, helps to characterize the risk. These processes ultimately inform risk management decisions.

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