November 27, 2015

Mr. Vytenis Andriukaitis
Commissioner Health & Food Safety
European Commission
Rue de la Loi / Wetstraat 200
1049 Brussels
Belgium

Cc: (email only)
- Mr. Phil Hogan, European Commissioner for Agriculture and Human Development
- Dr. Ladislav Miko, Deputy Director-General, DG Health & Food Safety
- Dr. Bernhard Url, Executive Director, EFSA
- Dr. Giovanni La Via, Chair, ENVI Committee
- EFSA Panel on Plant Protection Products and their Residues
- Mr. Christian Schmidt, Minister of Food and Agriculture
- Dr. Helmut Tschiersky, President of the Federal Office of Consumer Protection and Food Safety (BVL)
- Professor Dr. Dr. Andreas Hensel, President, BFR
- Dr. Christopher Wild, Director, IARC
- Mr. Jim Jones, Assistant Administrator, USEPA

Open letter: Review of the Carcinogenicity of Glyphosate by EFSA and BfR

Dear Commissioner Andriukaitis,

We are a group of independent academic and governmental scientists from around the world who have dedicated our professional lives to understanding the role of environmental hazards on cancer risks and human health. We have banded together and write to you at this time to express our deep concern over the recent European Food Safety Agency (EFSA) decision[1] that the widely used herbicide, glyphosate "is unlikely to pose a carcinogenic hazard to humans." We ask that you forward the letter to the representatives of all EU member states before the next meeting of the Standing Committee on Plants, Animals, Food and Feed (December 10/11).

The EFSA decision, based upon the Renewal Assessment Report[2] provided by the German Federal Institute for Risk Assessment (BfR), runs counter to the finding earlier this year by the International Agency for Research on Cancer (IARC), the highly respected cancer arm of the World Health Organization that glyphosate is a *probable human carcinogen*. This IARC classification is based on a comprehensive assessment of the peer-reviewed toxicologic and epidemiologic literature undertaken over a 12-month period by a Working Group of 17 independent expert scientists. The IARC review linked glyphosate to dose-related increases in malignant tumors at multiple anatomical sites in experimental animals and to an increased incidence of non- Hodgkin lymphoma in exposed humans.

We reviewed these two differing decisions on the human carcinogenicity of glyphosate and conclude that the IARC WG decision is by far the more credible. The IARC WG decision was reached relying on open and transparent procedures by independent scientists who completed thorough conflict-of-interest statements and were not affiliated or financially supported in any way by the chemical manufacturing industry. It is fully referenced and depends entirely on reports published in the open, peer-reviewed biomedical literature. It is part of a long tradition of deeply researched and highly credible reports on the carcinogenicity of hundreds of chemicals issued over the past four decades by IARC and used today by international agencies and regulatory bodies around the world as a basis for risk assessment, regulation and public health policy.

In contrast, the BfR decision is not credible because it is not supported by the evidence and it was not reached in an open and transparent manner.

Accordingly, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature.

The IARC Working Group Decision

The International Agency for Research on Cancer (IARC) Monographs Programme identifies environmental causes of cancer in humans and has evaluated more than 950 agents since 1971. The Monographs Programme evaluates chemicals, drugs, mixtures, occupational exposures, lifestyles and personal habits, physical agents and biological agents. Monographs are written by an ad hoc Working Group (WG) of international scientific experts over a period of about 12 months ending in an eight-day meeting. The WG evaluates all of the publically-available scientific literature on a given substance and, through a transparent and rigorous process[3], reaches a decision on the degree to which the scientific evidence supports that substance's ability to cause or not cause cancer.

For Monograph 112[4], 17 expert scientists evaluated the carcinogenic hazard for 4 insecticides and the herbicide glyphosate[5]. The WG concluded that the data for glyphosate meets the criteria to be identified as a *probable human carcinogen*. This finding stirred great debate globally on the safety of glyphosate and led to a careful evaluation by numerous agencies of the IARC monograph results when they became available on July 29, 2015.

The BfR Addendum

In October, 2015, the EFSA reported[1] on their evaluation of the Renewal Assessment Report[2] (RAR) for glyphosate. EFSA concluded that "glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential". Addendum 1 (the BfR Addendum) of the RAR[2] discusses the scientific rationale for differing from the IARC WG conclusion.

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We have serious concerns with regard to the scientific evaluation in the BfR Addendum and feel that it is misleading regarding the potential for a dose-dependent carcinogenic hazard from exposure to glyphosate. Since the BfR Addendum is the basis for the European Food Safety Agency (EFSA) conclusion[1], it is critical that we express these concerns. We are also concerned about some of the implications of the BfR Addendum regarding the use of human data in identifying carcinogenic hazards.

Our comments to the BfR Addendum will focus on the human evidence, the animal laboratory evidence and the mechanistic evidence.

The Human Evidence

The BfR agrees with the IARC WG that there is "*limited evidence* in humans for the carcinogenicity of glyphosate". In the IARC review process, *limited evidence* is assigned if "A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence."[3] The EFSA conclusion that "glyphosate is unlikely to pose a carcinogenic hazard to humans" is inappropriate when available data support the determination of *limited evidence* of carcinogenicity in humans. The BfR Addendum (p. ii) characterizes the IARC interpretation as "precautionary" and that the BfR takes a more "cautious view" of this classification because "no consistent positive association was observed", "the most powerful study showed no effect" and that the studies "could not differentiate between the effects of glyphosate and the co-formulants". We will consider the first two arguments here and discuss the third argument at the end of this letter.

The finding of *limited evidence* by the IARC WG was for non-Hodgkin lymphoma (NHL). High-quality cohort studies are particularly valuable for determining the carcinogenicity of an agent because their design can facilitate exposure assessment and reduce the potential for certain biases. The Agricultural Health Study[6] (AHS) was the only cohort study available providing information on the carcinogenicity of glyphosate. The study had a null finding for NHL (RR 1.1, 0.7-1.9) with no apparent exposure response in the results. The BfR refers to this study as "the most powerful study" and notes that it was "negative" for NHL.

Several potential limitations of case-control studies are laid out in epidemiology textbooks[7, 8]. The BfR uses these limitations to label all of the case-control studies as unreliable. This gives the impression that all of the studies are equal in quality and unusable for an overall evaluation. This is not the case: well-designed case-control studies are recognized as an efficient alternative to cohort studies[8]. An IARC WG carefully evaluates all of the available epidemiology data, looking at the study's strengths and weaknesses. This is key to determining whether the positive associations seen in case-control studies are a reliable indication of an association or simply due to chance or methodological flaws. To provide a reasonable interpretation of the findings, an evaluation needs to properly weight studies according to their quality rather than simply count the number of positives and negatives. The meta-analyses cited in the IARC Monograph[9] and done by the WG

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are excellent examples of an objective evaluation of the existence of a consistent positive association; both meta-analyses showed a statistically significant association. The BfR provided no justification for their evaluation of "no consistent positive association". Finally, despite the potential advantages of prospective cohort studies versus case-control, there are fewer cases to include in analyses, depending on the follow-up time resulting in limited statistical power. There were only 92 NHL cases included in the AHS unadjusted analysis and fewer in adjusted analyses, compared to 650 in a pooled case-control analysis from the United States[10].

The final BfR conclusion (p. 21) that "there was no unequivocal evidence for a clear and strong association of NHL with glyphosate" is misleading. IARC, like many other groups, uses three levels of evidence for human data[3]. *Sufficient evidence* means "that a causal relationship has been established" between glyphosate and NHL. IARC does not state that the evidence is *sufficient*. BfR concludes that the IARC designation of *limited evidence* was not applicable because there was not "an unequivocal and consistent excess". In fact, that is the equivalent to the criteria for *sufficient evidence*, not *limited evidence*. Thus BfR's conclusion is equivalent to concluding there is not *sufficient evidence*. Legitimate public health concerns arise when "causality is credible", i.e., when there is *limited evidence*. BfR's language is misleading and not internationally acceptable and thus fails to meet EC Guidelines.

Evidence from Animal Carcinogenicity Studies

We find the conclusions of the BfR regarding the animal carcinogenicity data to be scientifically unacceptable. The IARC WG review found a significant positive trend for renal tumors in CD-1 mice[11], a rare tumor although no comparisons of any individual exposure group to the control group were statistically significant. A significant positive trend means that the pattern seen in the data supports an increasing risk with increasing dose. The WG also identified a significant positive trend for hemangiosarcoma in male CD-1 mice[12], again with no individual exposure group significantly different from controls. Finally, the WG also saw a significant increase in the incidence of pancreatic islet cell adenomas in two studies in Sprague-Dawley rats[13-15]. In one of these rat studies, thyroid gland adenomas in females and liver adenomas in males were also increased. Thus, glyphosate was positive for malignant tumors in both of the mouse studies examined and for benign tumors in two of the five rat studies examined. By the IARC review criteria[3], the evidence in the mouse constitutes *sufficient evidence* in animals and the increased incidences of benign tumors constitutes additional support.

The BfR agreed, stating (p. 43) "it is obvious that IARC concludes on "*sufficient evidence* of carcinogenicity" because the above criteria for this conclusion are fully met." The IARC WG reached this conclusion using data that were publicly available in sufficient detail for independent scientific evaluation (a requirement of the IARC Preamble[3]). Based on the BfR Addendum, it seems there were three additional mouse studies and two additional rat studies that were unpublished but available for review. BfR reported on two additional studies with a positive trend for renal tumors, one in CD-1 mice[16], and one in Swiss-Webster mice[17]. One of these studies[16] also reported a positive trend for hemangiosarcoma. Moreover, BfR reported two studies in CD-1 mice showing significant trends for malignant

lymphoma[16, 18]. For all of the mouse tumors described above, a positive trend was seen against the concurrent control.

However, in all studies in CD-1 mice, including those reviewed by the IARC, the BfR dismisses the observed trends in tumor incidence because there are no individual treatment groups that are significantly different from controls and because the maximum observed response is reportedly within the range of the historical control data (Table 5.3-1, p. 90). Care must be taken in using historical control data to evaluate animal carcinogenicity data. In virtually all guidelines[3, 19], scientific reports[20] and publications[21-23] on this issue, the recommended first choice is the use of the concurrent controls. For instance, the Preamble to the IARC Monographs states, "it is generally not appropriate to discount a tumor response that is significantly increased compared with concurrent controls by arguing that it falls within the range of historical controls…". When using historical control data, they should be from studies in the same timeframe, for the same exact animal strain, preferably from the same laboratory or the same supplier and preferably reviewed by the same pathologist[19]. This was not the case for the historical control database used by BfR. One of the mouse studies[11] was clearly done before this historical control database was developed, one study[16] used Crj:CD-1 mice rather than Crl:CD-1 mice, and one study[12] did not specify the substrain and was reported in 1993 (probably started prior to 1988); hence only a single study[18] used the same mouse strain as the historical controls, but was reported more than 10 years after the historical control dataset was developed. Interestingly, the historical control data used by the BfR[24] was from studies in seven laboratories using the Charles River Laboratory CD1 mice. It is important to note that there is a second report[25] by the same authors with a larger control database using the same mouse strain from 11 laboratories over the same time period (1987-2000) showing very different results. For example, the 2000 publication[24] shows five and four studies out of 46 with renal adenomas (no more than two in any one study) and renal adenocarcinomas (one in each study) respectively whereas the 2005 report[25] shows only one study each out of 54 studies with a single renal adenoma and a single renal adenocarcinoma; all other studies had no renal tumors.

Given this evidence, it is clear that BfR differed from standard scientific practices in order to reach their conclusions. BfR reported seven positive mouse studies with three studies showing increases in renal tumors, two with positive findings for hemangiosarcomas, and two with positive findings for malignant lymphomas. BfR additionally reported two positive findings for tumors in rats. Eliminating the inappropriate use of historical data, the unequivocal conclusion is that these are not negative studies, but in fact document the carcinogenicity of glyphosate in laboratory animals.

Mechanistic Information

The BfR Addendum dismisses the WG finding that "there is strong evidence that glyphosate causes genotoxicity" by suggesting that unpublished evidence not seen by the IARC WG was overwhelmingly negative and that, since the studies that were reviewed were not done under guideline principles, they should get less weight. To maintain transparency, IARC reviews only publicly available data. Thus the use of confidential data submitted to the BfR makes it impossible for any scientist not associated with BfR to review this conclusion with scientific

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confidence. Further skewing their interpretation, the BfR did not include evidence of chromosomal damage from exposed humans[24] that was highlighted in the IARC Monograph.

The BfR confirms (p. 79) that the studies evaluated by the IARC WG on oxidative stress were predominantly positive but does not agree that this is strong support for an oxidative stress mechanism. They minimize the significance of these findings predominantly because of a lack of positive controls in some studies and because many of the studies used glyphosate formulations and not pure glyphosate. The WG concluded that (p. 77) "Strong evidence exists that glyphosate, AMPA and glyphosate-based formulations can induce oxidative stress". From a scientific perspective, these types of mechanistic studies can play a key role in distinguishing between the effects of mixtures, pure substances and metabolites and we encourage the BfR to carefully review this science.

Finally, we strongly disagree that data from studies published in the peer-reviewed literature should automatically receive less weight than guideline studies. Once a chemical or its formulations are on the market, the majority of the research done on these chemicals will be done by research laboratories using various models to address specific issues related to toxicity that will often not have testing guidelines associated with them. These peer-reviewed and published findings have great value in understanding mechanisms of carcinogenicity and should be given appropriate weight in an evaluation based on study quality and not just guideline rules.

General Comments

Science moves forward based on data, careful evaluation of those data and a rigorous review of the findings and conclusions. One important aspect of this process is transparency and the ability to question or debate the findings of others. This ensures the validity of the results and provides a strong basis for decisions. Many of the aspects of transparency do not exist for the RAR[2] or the BfR Addendum. For example, citations for almost all of the references, even those from the open scientific literature, have been redacted from the document. The ability to objectively evaluate the findings of a scientific report requires a complete list of the cited supporting evidence. As another example, there are no authors or contributors listed for either document, a requirement for publication in virtually all scientific journals. This is in direct contrast to the IARC WG evaluation listing all authors, all publications and public disclosure of pertinent conflicts of interest prior to the WG meeting[26].

A second important aspect of the scientific process is a careful evaluation and analysis of the facts. Several guidelines have been devised for analyzing carcinogenicity data, most after consultation with scientists from around the world. One of the most widely used guidelines is the OECD guidance on the conduct and design of chronic toxicity and carcinogenicity studies[19] which is cited in the BfR Addendum. This OECD guidance is in contradiction to the methods used by the BfR for both historical controls and for trend analysis; the two reasons given by the BfR for dismissing these data. Thus, BfR uses the

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concept of testing guidelines to exclude substantive scientific evidence from their risk assessment and ignore OECD guidelines in addressing the important issues of historical controls and trend analyses.

Due to the potential public health implications of this extensively used pesticide it is essential that all scientific evidence be freely available, reviewed openly in an objective manner, and that financial support, conflicts of interest and affiliations of authors be fully disclosed. Many aspects of the evaluation conducted by the BfR and EFSA do not meet this fundamental objective criteria and raise significant questions of validity.

Summary

The IARC WG concluded that glyphosate is a "probable human carcinogen" putting it into IARC category 2A due to *sufficient evidence* of carcinogenicity in animals, *limited evidence* of carcinogenicity in humans and *strong* mechanistic data.

- The IARC WG found an association between non-Hodgkin lymphoma and glyphosate based on the available human evidence.
- The IARC WG found significant carcinogenic effects in laboratory animals for two tumor types in two mouse studies and benign tumors in two rat studies.
- Finally, the IARC WG concluded strong evidence of genotoxicity and oxidative stress for glyphosate, entirely from publicly available research, including findings of DNA damage in the peripheral blood of exposed humans.

In their RAR, BfR concluded (Vol. 1, p. 160) "classification and labeling for carcinogenesis is not warranted" and "glyphosate is devoid of genotoxic potential".

- BfR agreed with the IARC on *limited evidence* in humans but then dismissed the association as "insufficiently consistent" with no justification.
- Using an inappropriate historical control dataset in an incorrect manner and ignoring established OECD guidelines cited in their report, BfR dismissed evidence of renal tumors in 3 mouse studies, hemangiosarcoma in 2 mouse studies and malignant lymphoma in 2 mouse studies. Thus, BfR incorrectly discarded all of the glyphosate-induced carcinogenic findings in animals as chance occurrences.
- The BfR ignored important laboratory and human evidence of genotoxicity.
- The BfR confirmed that glyphosate induces oxidative stress and dismissed this finding for lack of any other finding because they had dismissed all of the other evidence.

The most parsimonious scientific explanation of the cancers seen in humans and laboratory animals supported by the mechanistic data is that glyphosate is a *probable* human carcinogen. On the basis of this conclusion and in the absence of

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contrary evidence, it is reasonable to conclude that glyphosate formulations should also be considered probable human carcinogens.

We believe that the arguments promoted by the BfR to negate the human, animal and mechanistic evidence are fundamentally and scientifically flawed and should be rejected. We strongly object to the almost non-existent weight given to studies from the literature by the BfR and the strong reliance on non-publicly available data in a limited set of assays that define the minimum data necessary for the approval of a pesticide. We believe that the IARC WG evaluation of *probably carcinogenic to humans* accurately reflects the results of the published scientific literature on glyphosate and, on the face of it, the unpublished studies to which the BfR refers. Conversely, the BfR evaluation, and consequently the EFSA evaluation, do not reflect the available science.

Thus, repeating our earlier request, we urge you and the European Commission to disregard the flawed EFSA finding on glyphosate in your formulation of glyphosate health and environmental policy for Europe and to call for a transparent, open and credible review of the scientific literature.

The views expressed in this letter are the opinion of the scientists who are listed below and DO NOT imply an endorsement or support for these opinions by any organizations to which they are affiliated.

Sincerely,

Prof. Christopher J. Portier (Corresponding Author)
Senior Contributing Scientist, Environmental Defense Fund, Washington, DC
Visiting Professor, Maastricht University, Maastricht, The Netherlands
Adjunct Professor, Emory University, Atlanta, Georgia, USA
Honorary Professor, University of Queensland, Brisbane, Queensland, Australia
Former Director, National Center for Environmental Health, Atlanta, USA
Former Director, Agency for Toxic Substances and Disease Registry, Atlanta, USA
Former Associate Director, US National Toxicology Program, RTP, NC, USA
CH-3600 Thun, Switzerland
cportier@mac.com
+41 79 605 7958

Bruce Armstrong MBBS, DPhil(Oxon), FFAPHM, FAA
Emeritus Professor
Sydney School of Public Health
The University of Sydney, Australia

Distinguished Professor Bruce C Baguley
Auckland Cancer Society Research Centre
The University of Auckland
Auckland, New Zealand

Prof. Dr. med. Xaver Baur
Institute for Occupational Medicine

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Charité University Medicine Berlin
14195 Berlin , Germany

Igor Beliaev, PhD, DrSc
Associate Professor of Genetic Toxicology
Head, Laboratory of Radiobiology
Cancer Research Institute
Slovak Academy of Science
Bratislava, Slovak Republic
and
Professor, Laboratory of Radiobiology
Department of Ecological and Medical Problems
Prokhorov General Physics Institute
Russian Academy of Science
Moscow, Russia

Professor Robert Bellé
Laboratoire de Biologie intégrative des modèles marins (UMR 8227, CNRS-UPMC)
Université Pierre et Marie Curie
Station Biologique
29680 Roscoff France

Dr. Fiorella Belpoggi
Director
Cesare Maltoni Cancer Research Center
Ramazzini Institute
40010 Bentivoglio (Bologna), Italy

Prof. Annibale Biggeri
Director Biostatistics Unit
Institute for Cancer Prevention and Research
Department of Statistics Computer Science Applications "G. Parenti"
University of Florence, Italy

Maarten C. Bosland, DVSc, PhD
Professor of Pathology
Department of Pathology
College of Medicine
University of Illinois at Chicago
Chicago, IL 60612 USA

Prof. Paolo Bruzzi MD, MPH, PhD
Director, Unit of Clinical Epidemiology
National Cancer Research Institute
San Martino – IST Hospital
Genoa ITALY

Prof. Dr. Lygia Therese Budnik

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University of Hamburg, Hamburg, Germany
European Society for Environmental and Occupational Medicine.

Dr. Merete D. Bugge, PhD
Senior Physician
STAMI, National Institute of Occupational Health
Oslo, Norway

Kathleen Burns, PhD
Director
Sciencecorps
Lexington, MA, USA

Gloria M. Calaf Ph. D.
Director, Instituto de Alta Investigación
Universidad de Tarapacá
Arica-Chile
and
Adjunct Associate Research Scientist
Columbia University Medical Center
Center for Radiological Research
New York, New York USA

David O. Carpenter, M.D.
Director, Institute for Health and the Environment University at Albany
Rensselaer, NY 12144 USA

Hillary M. Carpenter, Ph.D., Toxicologist
Minnesota Department of Health, Retired
Maplewood MN 55109 USA

Lizbeth López-Carrillo
Senior Researcher
National Institute of Public Health
Cuernavaca, Morelos, Mexico

Prof. Richard Clapp
Professor Emeritus
Boston University School of Public Health
Boston, MA USA

Prof. Pierluigi Cocco, M.D.,HonFFOM
Chair, Occupational Medicine
Department of Public Health, CLinical and Molecular Medicine
University of Cagliari, Italy

Pietro Comba, PhD,
Head , Unit of Environmental Epidemiology
Department of Environment and Primary Prevention

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Istituto Superiore di Sanità, Rome, Italy

Dr Dario Consonni, MD, MPH, PhD
Occupational Physician and Epidemiologist
Epidemiology Unit, Department of Preventive Medicine
Fondazione IRCCS Ca' Granda - Ospedale Maggiore Policlinico
Milan, Italy

Devra Davis, Md, PhD
Visiting Professor, The Hebrew University, Hadassah Medical School, Jerusalem
Visiting Professor, Ondukuz Mayis University Medical School, Samsun, Turkey
President, Environmental Health Trust
Jackson Hole, WY USA

Anneclaire De Roos, MPH, PhD
Associate Professor
Environmental & Occupational Health
Dornsife School of Public Health
Drexel University
Philadelphia, PA USA

Paul A. Demers, Ph.D.
Director
Occupational Cancer Research Centre, Cancer Care Ontario
Professor
Dalla Lana School of Public Health, University of Toronto
Toronto, Canada

Dr. Jamie DeWitt
Associate Professor of Pharmacology & Toxicology
Brody School of Medicine, East Carolina University
Greenville, NC, USA

Dr. Francesco Forastiere
Director Etiological and Analytical Epidemiology
Department of Epidemiology, Lazio Regional Health Service
Rome, Italy

Dr. Jonathan H Freedman, Ph.D.
Professor, Department of Pharmacology and Toxicology
University of Louisville School of Medicine
Louisville, Kentucky 40202 USA

Prof. Lin Fritschi
School of Public Health, Curtin University
Perth, Australia

Dr. Caroline Gaus Associate Professor
Environmental Toxicology

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The University of Queensland
Brisbane, Australia

Julia M Gohlke, PhD
Assistant Professor
Department of Population Health Sciences
Virginia-Maryland College of Veterinary Medicine
Virginia Tech
Blacksburg, VA 24061-0395, USA

Professor Marcel Goldberg
Emeritus Professor of epidemiology
Paris Descartes University
Paris, France.

Prof. Eberhard Greiser
Emeritus Professor of epidemiology and medical statistics
Associate Professor, Center for Social Policy Research, Bremen University,
CEO, Epi.Consult GmbH, Musweiler, Rhineland-Palatinate, Germany.

Prof. Per Gustavsson, MD
Head of Unit of Occupational Medicine
Institute of Environmental Medicine, Karolinska Institute
Centre for Occupational and Environmental Medicine, Stockholm County Council
Stockholm, Sweden

Dr. Johnni Hansen
Senior Scientist
Danish Cancer Society Research Center
Copenhagen, Denmark

Dr. Lennart Hardell, MD, PhD
Department of Oncology
University Hospital
Orebra, Sweden

Dr. Michael Hauptmann
Head, Biostatistics Branch
Netherlands Cancer Institute
Amsterdam, The Netherlands

Wei Huang, ScD (HSPH 2003)
Professor, Peking Univ School of Public Health
Vice Director, Peking Univ Institute of Environmental Medicine
Key Lab of Molecular Cardiovascular Research Ministry of Education
Beijing, China, 100191

James Huff, PhD
Formerly, Associate Director For Chemical Carcinogenesis

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National Institute Of Environmental Health Sciences
Research Triangle Park, North Carolina USA

Professor Margaret O. James
Jack C. Massey Professor of Pharmacy, Professor of Medicinal Chemistry
University of Florida
Gainesville, Florida USA

C W Jameson, PhD
CWJ Consulting, LLC
Retired Director for the Report on Carcinogens
National Toxicology Program/National Institute of Environmental Health Sciences
National Institutes of Health
Cape Coral, FL USA

Professor Andreas Kortenkamp
Human Toxicology
Institute of Environment, Health and Societies
Brunel University London
Uxbridge, UB8 3PH, United Kingdom

Prof. Dr. Annette Kopp-Schneider
Head of Div. Biostatistics
German Cancer Research Center
69120 Heidelberg, Germany

Professor Hans Kromhout
Chair in Exposure Assessment and Occupational Hygiene
Chair in Epidemiology of Health Effects of Electromagnetic Fields
Division of Environmental Epidemiology
Institute for Risk Assessment Sciences
Utrecht University
Utrecht, The Netherlands

Prof. Marcelo L. Larramendy, Ph.D.
Principal Researcher National Council of Scientific and Technological Research (CONICET)
School of Natural Sciences and Museum
National University of La Plata
La Plata, Argentina

Philip J. Landrigan, MD, MSc, FAAP
Dean for Global Health
Arnhold Institute for Global Health
Professor of Preventive Medicine & Pediatrics
Icahn School of Medicine at Mount Sinai
New York, NY 10029 USA

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Lawrence H. Lash, Ph.D.
Professor and Associate Chair
Department of Pharmacology
Wayne State University School of Medicine
Detroit, MI 48201 USA

Dariusz Leszczynski, PhD, DSc
Adjunct Professor
Department of Biosciences
Division of Biochemistry & Biotechnology
University of Helsinki, Finland

Prof. Charles F. Lynch, MD, PhD
Department of Epidemiology
College of Public Health
University of Iowa
Iowa City, IA, USA

Prof. Corrado Magnani MD
Professor of Medical Statistics
Head of the Cancer Epidemiology Unit
University of Eastern Piedmont
Novara, Italy

Daniele Mandrioli, MD
Associate Director
Cesare Maltoni Cancer Research Center
Ramazzini Institute
40010,Bentivoglio (Bologna), Italy

Francis L Martin
Centre for Biophotonics, LEC, Bailrigg
Lancaster University
Lancaster LA1 4YQ, UK

Dr. Ron Melnick, PhD
Ron Melnick Consulting, LLC
Retired Senior Toxicologist
National Toxicology Program/
National Institute of Environmental Health Sciences
National Institutes of Health
Chapel Hill, NC USA

Dr. Enzo Merler, PhD
Director
Rgional Registry on Mesothelioma, Veneto Region, Italy
Department of Prevention, Occupational Health Unit
National Health Service
Padua, Italy

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Paola Michelozzi
Director Environmental Epidemiology Unit
Department of Epidemiology Lazio Region
Rome, Italy

Dr. Lucia Miligi,
Senior Epidemiologist,
Occupational and Environmental Epidemiology Unit,
ISPO-Cancer Prevention and Research Institute,
Florence, Italy

Anthony B. Miller, MD
Professor Emeritus
Dalla Lana School of Public Health, University of Toronto
Toronto, Canada

Dr. Dario Mirabelli
Epidemiologist
Unit of Cancer Epidemiology, University of Turin and CPO-Piemonte
10126 Torino Italy

Franklin E. Mirer, PhD, CIH
Professor, Environmental and Occupational Health Sciences
City University of New York School of Public Health
New York, NY 10035 USA

Michael M. Müller, PhD
EUROTOX Registered Toxicologist
Head of the Toxicological Laboratory Unit
Department of Occupational, Social and Environmental Medicine
University Medical Center Göttingen
37073 Göttingen Germany

Dr Saloshni Naidoo (MBChB, FCPHM, MMed, PHD)
Chief Specialist / Head of Discipline
Public Health Medicine
School of Nursing and Public Health
University of KwaZulu-Natal
Durben, South Africa

Prof. Melissa J. Perry, ScD, MHS, FACE
Professor and Chair of Environmental and Occupational Health
Professor of Epidemiology
Milken Institute School of Public Health
Professor of Biochemistry and Molecular Biology
School of Medicine and Health Sciences
The George Washington University
Washington, DC 20051 USA

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Dr. Maria Grazia Petronio
Head of Unit of Health and Environment-Department of Prevention
Local Health Authority-Empoli, Florence, Italy
Professor of Environmental Hygiene
School of Specialization "Hygiene and Preventive Medicine
University of Pisa, Italy
Vice-President for Central Italy Area of International Society of Doctors for Environment, Italy

Dr Roberta Pirastu
Researcher
Department of Biology and Biotechnology "Charles Darwin"
Sapienza Rome University, Italy

Prof. Miquel Porta, MD, MPH, PhD
Professor and Senior Scientist, Hospital del Mar Institute of Medical Research (IMIM) and School of Medicine
Universitat Autònoma de Barcelona
Barcelona, Catalonia, Spain

Ralph J. Portier, PhD
Distinguished Professor of Environmental Sciences
Department of Environmental Sciences, School of the Coast & Environment
Louisiana State University
Baton Rouge, LA 70803 USA

Kenneth S Ramos, MD, PhD, PharmB
Associate Vice President for Precision Health Sciences
Professor of Medicine
Director of Center for Applied Genetics and Genomic Medicine
University of Arizona Health Sciences
Tucson AZ. 85737 USA

Larry W. Robertson, MPH, PhD, ATS
Professor and Director, Iowa Superfund Research Program and the Interdisciplinary
Graduate Program in Human Toxicology
The Univerity of Iowa
Iowa City, Iowa, USA

Martin Röösli, PhD
Head of the Environmental Exposures and Health Unit
Swiss Tropical and Public Health Institute
Associated Institute of the University of Basel
4002 Basel, Switzerland

Matt K. Ross, PhD
Associate Professor

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College of Veterinary Medicine
Mississippi State University
Mississippi State, MS 39762 USA

Prof. Deodutta Roy, MS, M.Phil., Ph.D.
Department of Environmental and Occupational Health
Robert Stempel College of Public Health and Social Work
Florida International University
Miami, FL 33199-0001 USA

Ivan Rusyn, MD, PhD
Professor, Veterinary Integrative Biosciences Texas A&M University
College Station, TX 77843-4458 USA

Paulo Saldiva, MD, PhD
Professor of Pathology, Faculty of Medicine,
University of São Paulo, Brazil
Coordinator of the National Institute of Integrated Risk Assessment
National Research Council, Brazil

Jennifer Sass, PhD
Senior Scientist Natural Resources Defense Council and
Professorial Lecturer, George Washington University
Washington, DC USA

Kai Savolainen, MD, Ph.D., Research Professor
Director, Nanosafety Research Centre
Finnish Institute of Occupational Health
Helsinki, Finland

Assoc Prof. Paul T.J. Scheepers, PhD, ERT
Workgroup Leader and Head, Research Lab Molecular Epidemiology
Radboud Institute for Health Sciences
Radboud University Medical Center
Nijmegen, The Netherlands

Prof. Dr. Consolato Sergi, MSc, MD, PhD, FRCPC
Full Professor of Pathology and
Full Professor of Pediatrics (Adjunct)
University of Alberta,
Edmonton, Alberta, Canada

Ellen K Silbergeld, PhD
Professor, Environmental Health Sciences
Johns Hopkins Bloomberg School of Public Health
Baltimore MD 21205 USA

Prof. Martyn T. Smith
School of Public Health

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University of California, Berkeley
Berkeley, CA USA

Prof. Bernard W. Stewart
Faculty of Medicine, University of New South Wales
Head, Cancer Control Program South East Sydney Public Health Unit
Randwick NSW 2031 Australia

Patrice Sutton, MPH
Research Scientist
University of California, San Francisco, Program on Reproductive Health and the Environment
San Francisco, USA

Dr. Fabio Tateo
Researcher
Istituto di Geosceinze e Georisorse (CNR)
35131 Padova, Italy

Prof. Benedetto Terracini
Professor of Cancer Epidemiology (retired)
University of Torino
Torino, Italy

Prof. Dr. med. Dr. rer. nat. Heinz W. Thielmann
Former Division Head at the German Cancer Research Center, Heidelberg
Retired Prof. of Biochemistry, Faculty of Pharmacy, Heidelberg University
Member of Committee on Health Hazards of Chemicals of the Deutsche Forschungsgemeinschaft
Germany

David B. Thomas, MD, DrPH
Prof Emeritus, School of Public Health and Community Medicine
University of Washington
and
Member, Fred Hutchinson Cancer Research Center
Seattle, WA, U.S.A.

Prof. Harri Vainio
Professor of Environmental and Occupational Health
Dean-Elect
Faculty of Public Health, Kuwait University, Kuwait
Kuwait City, Kuwait

John E. Vena, Ph.D.
Professor and Founding Chair
Department of Public Health Sciences
Medical University of South Carolina
Charleston SC 29425 USA

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Professor Paolo Vineis
Chair in Environmental Epidemiology
Imperial College London, UK

Professor Elisabete Weiderpass, M.D., M.Sc., Ph.D.
Head - Department of Research
Head - Group of Etiological Cancer Research
Institute of Population Based Cancer Research
Cancer Registry of Norway, Oslo, Norway
Department of Community Medicine, Faculty of Health Sciences
University of Tromsø, The Arctic University of Norway, Tromsø, Norway
Department of Medical Epidemiology and Biostatistics
Karolinska Institutet, Stockholm, Sweden
Genetic Epidemiology Group
Folkhälsan Research Center, Helsinki, Finland

Dennis D. Weisenburger, M.D.
Professor/Chair, Department of Pathology
City of Hope Medical Center
Duarte, CA 91010 USA

Professor Tracey J. Woodruff, PhD, MPH
Director
University of California, San Francisco, Program on Reproductive Health and the Environment
San Francisco, USA

Prof. Dr. rer. nat. Irene Witte (retired)
Institute for Biology and Environmental Sciences
University of Oldenburg
Germany

Dr. Takashi Yorifuji
Associate Professor
Okayama University
Okayama, Japan

Il Je Yu, PhD, Professor
Director, Institute of Nanoproduct Safety Reserch
Hoseo Universtiy,
Asan, Korea

Dr. Paola Zambon
Past Director Veneto Tumor Registry
University of Padua
Padova Italy

Prof. Dr. Hajo Zeeb

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Head, Department of Prevention and Evaluation, Leibniz-Institute for Prevention Research and Epidemiology - BIPS
Bremen, Germany

Prof. Shu-Feng Zhou, MD, PhD
Associate Dean for International Research and Chair
College of Pharmacy
University of South Florida
Tampa, Florida, USA

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