Proceedings of the Workshop on
Conducting Evaluations of Evidence that are
Transparent, Timely and Lead to Health-Protective Actions

February 8-11, 2021

Hosted by: David Gee (Brunel University London, UK), **Jennifer Sass** (Natural Resources Defense Council, and George Washington University, USA), **Nicholas Chartres** (University of California San Francisco, USA)

With support from: **Olwenn Martin** and **Andreas Kortenkamp** (Brunel University), **Christina Ruden** (Stockholm University)

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Scientists have often evaluated the same evidence on hazardous agents very differently causing confusion amongst policymakers, politicians, and the public as well as controversies between scientists, as the COVID-19 pandemic demonstrates. The focus of the workshop will be on reasons for the divergent evaluations, and how to minimize and render them more transparent, consistent, and supportive of timely action.

AGENDA

Day 1, Monday Feb 8th

Welcome, Introductions & Objectives of the Workshop. Nicholas Chartres, Jennifer Sass

Session 1 - Coaxing causality from complexity
Chair: **Matthieu Schuler** (Managing General Director of the Science for expertise Department, and Head, Risk Assessment Division, ANSES, France)

When science and policy fail high risk communities: a case study of hexavalent chromium – **Mark Mitchell, MD, MPH, FACPM** (National Medical Assoc, USA)

Overcoming complexity and establishing causality in ATSDR investigations – **Patrick Breysse** (Director, NCEH/ATSDR, USA)

Decision-making under uncertainty and ignorance – **Christopher Portier** (Ret Director US NTP, Switzerland)

Breakout Question – How do we establish sufficient strength of evidence for timely action, that avoids unacceptable consequences?
Breakout discussion leaders: Jennifer Sass, Patrick Breysse, Christopher Portier, Matthieu Schuler

Report back from breakout groups, plenary discussion – Led by **Nicholas Chartres**

Wrap up, prep for next day **Jennifer Sass, Nicholas Chartres**

Day 1: Introduction & Rationale

Introduction and Rationale of the Workshop (Nicholas Chartres)

Approximately one quarter of all deaths globally are attributed to living or working in an unhealthy environment, with household and ambient air pollution, along with exposures to ultraviolet radiation and chemicals amongst the leading causative risk factors. While it is estimated that there are tens of thousands of chemicals approved for commercial use, the majority of these have not been assessed for toxicity. Typically, the highest chemical exposures are to workers and fenceline communities – those that live adjacent to or nearby hazardous facilities. These are disproportionately low-income and communities of color, intersecting issues of poverty, race, housing, and occupational health hazards.

There are a number of challenges in conducting hazard identification and risk assessment of environmental hazards that are distinct from assessments of the effectiveness of clinical interventions. The first being that exposure is already occurring, and studies of health effects are primarily occurring after exposures occur. Further, exposures are not intended, precluding using experimental human studies to assess harms due to ethical considerations. The causal chain linking harmful substances with adverse outcomes is complex, with various interactions and often considerable time periods between exposure and effects. Hazardous substances may be comprised of many toxic components, with various interactions amongst them, making it difficult to identify the precise toxic component linked to an adverse health outcome. There are often multiple measures of

adverse health outcomes. For example, in assessing the toxicity of triclosan in non-human mammalian evidence, over 100 unique outcome measures were identified.

Several factors must be considered when assessing the risk of a hazard, including populations that are most susceptible (due to intrinsic biological factors) and vulnerable (due to environmental factors). Data required for hazard identification and risk assessment usually come from numerous data streams, including but not limited to: epidemiologic studies; animal toxicology studies; cellular and mechanistic studies. This can make assessments and synthesis of the evidence challenging. There is not yet consensus on how to assess the risk of bias in these studies in environmental health. Finally, while there has been numerous analyses and documented reports, there has not been a systematic review of the influence of industry sponsorship on research related to environmental hazards, including chemicals, and therefore its influence on the evidence base has not been fully measured, quantified, and thus understood.

Scientists, therefore, have often evaluated the "same" evidence on hazardous agents very differently causing confusion amongst policymakers, politicians, and the public as well as controversies between scientists, as the COVID-19 pandemic demonstrates. Use of heterogeneous methods to identify health risks posed by environmental hazards may reduce the level of confidence the public has in the assessments and hinder the decision-making process. Some prominent examples of divergent evaluations from environmental and public health that will be discussed during this Workshop include: hexavalent chromium; glyphosate; nitrogen dioxide; PFOA; fluoride; and radiofrequency radiation from mobile phones. Such divergent evaluations have also been the source of much media attention, doubt and confusion, and consequent policy drift. This is despite several groups developing methods and frameworks to address environmental health questions, including the assessment of environmental exposures and human health, by extending methods from clinical medicine. This began in the 1970s with the International Agency for Research on Cancer (IARC) Monograph Programme before being developed for the clinical fields in the early 90s. Over the past 25 years, decision-making in the clinical arena has relied on systematic reviews, which entail structured, transparent and consistent methods for evaluating clinical evidence, as a source of trusted, evidence-based advice providing best care for patients and informing billions of dollars of spending in healthcare.

To bridge between systematic reviews in environmental health and the clinical sciences, authoritative bodies, U.S. agencies, and academic scientists developed and implemented validated, peer-reviewed systematic review methods including University of California San Francisco's Navigation Guide (UCSF NavGuide), the U.S. National Toxicology Program's Office of Health Assessment and Translation method (NIEHS NTP-OHAT) and the Systematic Review and Integrated Assessment of endocrine disrupting chemicals (SYRINA). These methods were also recognized by the seminal National Academy of Sciences 2011 report, "Review of the Environmental Protection Agency's Draft IRIS Assessment of Formaldehyde", which concluded that a robust, systematic, and transparent methodology was necessary to improve understanding of environmental health evidence.

It has been proposed that these well-structured, flexible approaches that are not too prescriptive and account for scientific issues in the design, conduct and analysis of environmental epidemiological and animal toxicology studies will increase transparency and prevent the introduction of a systematic bias when drawing conclusions on environmental hazards. The use of scientifically robust and transparent methods to evaluate the evidence also allows the reasons for conflicting conclusions and opinions to be readily identified.

Goals of the Workshop (David Gee, Jen Sass)

In 2008 the European Environment Agency convened a workshop on establishing the main reasons for such divergent evaluations. It focused on the controversial issues of bisphenol A; ELF from power lines; RFR from mobile phones; and pesticides spray drift, on which the top two UK public bodies responsible for evidence evaluations, the Royal Commission on Environmental Pollution (now abolished) and the Advisory Committee of Pesticides debated their divergent evaluations of the pesticides spray evidence in public fora. Here we build on the work started during that event, adding and updated case studies to identify and discuss what methodological advancements and future needs are required to help move towards producing transparent and consistent evaluations of evidence that support advances in health protections for workers, communities, and consumers.

However, we recognize and acknowledge that this is not enough. Science is only one element of decision-making. Important additional considerations include structural racism, sexism, socioeconomic disparities, and other systems that uphold inequities and injustices. These will have a much greater impact on the ability to deliver the health protections that are human rights. While we acknowledge the limitations of our work together over the next four days, we are also hopeful that our efforts will support the important goal of this workshop, to facilitate <u>Conducting Evaluations of Evidence that are Transparent, Timely and Lead to Health-Protective Actions.</u> We know that work will not do itself – we must do it. We have planned for this workshop and our time together this week to be insightful and engaging, and that it will inform and advance the work we have left to do.

Next steps - We expect the outcome to be a published manuscript, planned over the next 6 months or so. We will stay connected with all invited speakers and breakout leaders as we go forward.

Day 2, Tuesday Feb 9th

Session 2 - Lessons Learned from Divergent Evaluations of Some Physical and Chemical agents
Chair: **Nicholas Chartres** (UCSF)

Some key differences in the ICNIRP and IARC evaluations of RF evidence. – **James Lin** (University of Illinois & Ed. Bioelectromagnetics, USA)

Divergent evaluations on NO2 toxicity: COMEAP (Committee on the Medical Effects of Air Pollutants) report on quantification of all-cause mortality based on associations with long-term average NO2 concentrations. – **Roy Harrison** (Birmingham University), **Alison Gowers** (Public Health England)

Different strengths of timely evidence needed in divergent social and political contexts: various case studies. – **Linda Birnbaum** (Ret Director NIEHS, USA)

Core beliefs, weights of evidence and handling uncertainties in risk assessment – PFOA case study. – **Theo Vermeire** (RIVM & Chair EU-SCHEER)

Breakout Question – What are the key sources of divergent evaluations and how can we minimize them for timely action?

Breakout discussion leaders: **Aditi Shah, Elisabeth Cardis, Linda Birnbaum, Roy Harrison, Jennifer Sass**

Report back from breakout groups, plenary discussion – Led by **Michael Kundi**

wrap up, prep for next day – **Jennifer Sass, Nicholas Chartres**

<u>Day 1 & 2 Summary</u>

Environmental Injustices
Opening talk by Dr. Mark Mitchell who presented a case study of Cr6 in neighborhood community whose residents are predominantly black, with a high level of poverty. Governments and others repeatedly fail these communities – early and ongoing community engagement can help address this failure. Other case study examples on this point were brought out in the chat and the breakout sessions.

Dr. Mitchell also pointed out that there is a lack of trust in the community health and environmental health physicians that know how to identify poisoning from hazardous materials. Others noted that it's very important to involve frontline professionals, physicians, GPs, community health workers etc.

Dr. Mitchell made the point that in their current form, risk assessments and regulations are often outdated, calibrated for healthy white males, and fail to incorporate the cumulative impacts/burden of psycho-social factors including systemic racism and poverty. Many workshop participants continued to build on the themes of 'citizen science', community engagement, and cumulative risk over the next two days.

Multiple exposures and cumulative impacts
The need to incorporate multiple hazardous exposures, psycho-social stressors, lack of access to health care, etc was emphasized by many participants. Dr. Yukyan Lam suggested that one way to get more health-protective outcomes and address structural racism is to look at a 'cumulative impacts/burden analysis' rather than a 'cumulative risk' analysis. See <u>NJ Law here</u>.

Divergence
Many participants noted that divergence of scientific perspective may often be differences between and even within disciplines, as well as with competing pressures including cultural, economic, and political (Max Aung, Elisabeth Cardis). Cases show that quite often scientific controversies about environmental health issues are convoluted by (implicit and hidden) core beliefs and normative value judgements from experts and by their professional paradigms (Theo Vermeire). Acknowledgement of divergences is more important than resolving them. (Theo Vermeire).

Other more specific sources include: role of biology; model divergence; use of historical v within experiment controls; statistical approaches; methods of analysis, study interpretation (Laura Vandenberg). Chris Portier emphasized the need for guidelines or frameworks that address how evidence is interpreted and integrated, and that need to be kept updated. This was echoed and expanded upon by many workshop participants (Tony Fletcher, Elisabeth Cardis, Kurt Straif)

Uncertainty
Chris Portier lifted up the problem of 'uncertainty' – not that we have it, but that it is interpreted by non-scientists, and sometimes also science experts, as maybe an outsized problem.

The lack of data and scientific uncertainty perpetuates environmental health disparities and can contribute to or uphold a racist system (Yukyan Lam). Science-informed public health; if you wait for the science, you may miss opportunities for public health interventions and protective actions.

Timely action

There is a spectrum of perspectives that exists within the population – we need to find justification for delivering the highest level of protection from uncertainty.

We can often act faster without precise risk estimates; hazard assessment is faster.

We can shift burden of proof to industry, as is done under the European Union chemical regulations, 'Registration, Evaluation, Authorisation and Restriction of Chemicals' (REACH).

The Precautionary Principle is a tool for timely action in cases where there is not a consensus on a clear conclusion. The Precautionary Principle is seen as a risk management tool for action in cases where scientific uncertainty cannot be reduced sufficiently based on the data available.

A class approach to chemicals may work – evaluating chemicals as part of a class, where some are more studied, and some are less studied - but it can also be scientifically complicated; it should be discussed in Guidelines.

Take actions that protect all the global citizens – need an international public health coalition – ensure that solutions don't transfer burden of exposure; solutions to benefit everyone.

Day 3, Wednesday Feb 10th

Session 3 – Systematic Reviews of Chemicals
Chair: **Bjorn Hansen** (ECHA Exec Dir-personal capacity)

Evidence synthesis, integration and evaluation: the case of Glyphosate and beyond. – **Kurt Straif** (ISGlobal and Boston College).

Governing complex risks when evidence is limited – from SOER2020 to the EU chemicals strategy for sustainability. – **Xenia Trier** (European Environment Agency)

Evaluating EDCs systematically: the SYRINA approach. – **Anna Beronius** (Karolinska Institutet, Sweden)

Towards transparent and consistent Systematic Review Processes in Hazard and Risk Assessments. – **Tracey Woodruff** (University of California San Francisco, PRHE, USA)

Breakout Question –What are the key elements of systematic evaluations of harmful agents and what are the barriers to their more widespread use by hazard and risk assessment committees?

Breakout discussion leaders: **Erik Millstone; Bjorn Hansen, Anna Beronius, Nicholas Chartres**, **Kurt Straif**, **Vince Cogliano**
Report back from breakout groups, plenary discussion – led by **Bjorn Hansen**

wrap up, prep for next day – **Nicholas Chartres, Tracey Woodruff**

Day 3 Summary

What are the key elements of systematic evaluations of harmful agents?

Stakeholder Influence
- Problem formulation needs stakeholder engagement from civil society and policy makers to better ensure that relevant and appropriate research and policy questions are pursued. It is important to keep in mind that engagement of the regulated community can introduce financial conflicts that may influence the research and policy outcomes.

Methods
- **Transparency:** If the process is fully documented and something is misinterpreted because of lack of expertise, it should be possible to identify the issue and correct it (good documentation does not necessarily guarantee good quality though).
- **A well-defined PECO statement** (in a pre stablished protocol): systematizes review objectives and the methods that will be used to answer the defined question/s.
    o You can you go back and retrospectively refine your protocol in a transparent way.
- **Meta-analysis:**
    o While not always possible or appropriate, they can increase the statistical power and precision of an effect estimate.
    o One advantage is the possibility of conducting a sensitivity analysis. Sensitivity analyses are valuable to explore if heterogeneity can be explained possibly turning unexplained inconsistency into new consistency - for example on risk of bias e.g. on financial conflict of interest or if you have concern about timing of exposure. It's quite easy to do sensitivity analysis in a transparent way.
    o Sensitivity analyses can perhaps illuminate the relative reliability of competing judgements.
- **Risk of Bias analysis:** makes you read the whole study - it forces you to systematically understand the strengths and limitations of the evidence base.
- **Strength of Evidence:** A (pre-defined) succinct bottom-line summary regarding the strength of the evidence levels should be provided.

Expertise that are required
- The correct balance of necessary expertise to conduct the review and answer the question is essential (e.g. methodologists, toxicologists, epidemiologist etc.).

Managing author COI/Industry Sponsorship
- Risk of bias tools that evaluate financial conflicts of interest should be used to evaluate how this bias may bias the systematic review results. There is an abundance of empirical evidence that demonstrates that even when controlling for the methodological quality of a study, studies sponsored by industry are more likely to have more favorable results than those without industry sponsorship. Therefore, risk of bias tools that do not consider financial conflicts of interest will not capture this bias.

What are the barriers to their more widespread use by hazard and risk assessment committees?

Methods
- Methods that have evolved from the clinical sciences such as GRADE, are not currently applicable to many questions that risk assessors face, while tools to evaluate risk of bias were often developed without subject matter expertise (e.g. from environmental epidemiology experts).
- Lack of consensus on the methods limits their use by researchers and authorities.
- The term systematic review is misused (different techniques/methods) the making it difficult for non experts to identify credible systematic reviews. It can be very politicised, as in the case of US EPA TSCA.

Expertise/Resources that are required
- Time to conduct them.
- Systematic review entails a high up-front prep cost that would be a hindrance to their wide uptake.
- Evidence synthesis requires expert groups with the sufficient interdisciplinary subject matter expertise. Requires extraordinary diversity of expertise in many cases.
- Very little training or education available on these methods, not broadly taught at MPH level.

Important consideration for the future of SRs

Alternate, Rigorous Methods
- There'll be times when it's not the correct tool e.g., emerging or rapidly-developing situation - so we therefore need to understand that different techniques can be used, otherwise some entities wanting to delay an outcome may say it has to be very lengthy, expert, gold-plated peer review process when there are other ways to come at the problem.
- Rapid Reviews to answer important questions in a timelier manner.

Validation of the Methods
- Very little validation of systematic reviews.
- We need a Systematic Review of Systematic Review methods, as many of them have yet to be evaluated or validated.

Asking the Right Questions
- We need to include in the question, what is the higher good for society? For example, in pesticides often the active ingredient is the primary focus of evaluation, and not the formulated product.

Refining Risk of Bias Tools
- Studies should not be excluded due to only one methodological limitation.
- Validation of tools is challenging and very energy/data intensive
- Need to distinguish between reliability (high inter-observer kappa) vs construct validity
- Risk of bias assessments typically focus on whether specific biases (confounding, selection bias, and information bias) are present, but do not usually assess the direction, magnitude, or overall importance of the various types of bias; where possible, this should be done. Information bias alone is unlikely to explain positive findings of studies with non-differential exposure misclassification.
- An empirically developed tool is required like those used in the clinical sciences

Committees/Working Groups
- We aren't very systematic about how we select our committees. Eligibility criteria for committees are not set out up front and there is selection bias in the committee participants. Committees tend to be selected with people that are familiar with each other, and it leaves out many perspectives, including other races, other countries and cultures, and people not as senior in their careers. Language barriers might be significant, and should be addressed so as to be more inclusive.

Day 4, Thursday Feb 11th

Session 4 - Future Needs
Chair: **Vince Cogliano**

The key characteristics of carcinogens – IARC perspective. – **Kathryn Guyton** (IARC Monographe Programme, France)

Application of high throughput data in regulatory decision-making – NGO perspective. – **Kristi Pullen-Fedinick** (Natural Resources Defense Council, USA)

Use of Biomonitoring data in hazard and risk assessment of PFCs. – **Marike Kolossa-Gehring** (UBA, Germany).

Future applications of key characteristics approaches. – **Martyn Smith** (UC Berkeley, USA)

Advancing evidence decision frameworks to address social equity, environmental justice, and stakeholder engagement. – **Susan Norris**

Breakout Question – What is needed to ensure that evidence evaluations are timely and support health and environmental justice?

Breakout discussion leaders: **Kathryn Guyton, Kristi Pullen-Fedinick, Martyn Smith, Marika Kolossa-Gehring, Vincent Cogliano**

Report back from breakout groups, plenary discussion – led by **Jennifer Sass**

wrap up – **Nicholas Chartres, Jennifer Sass**

Day 4 Summary

Breakout Question – **What is needed to ensure that evidence evaluations are timely and support health and environmental justice?**

Martyn Smith report back
- Scientists shouldn't make decision-making too complex, we need rigor, not rigor-mortis.
- How much information/toxicology/properties do we need to know? PFAS are persistent, is that enough to impose regulatory restrictions? How much epi/tox is needed? We should start to develop methodologies that allow us to make decisions on limited information.

- The political and social factors are critical and yet scientists don't have much control over these.
- Include advocates and community members on committees and panels; their perspective is critical.
- Develop more *in silico* and high throughput methods; need for chemicals, mixtures, and particulate matter
- Require a minimum set of info for all chemicals in commerce for the next 5 years.
- Proprietary info still a problem – need more access to this information.
- Need more publicly accessible and user-friendly online tools.

Kate Guyton report back
- What is the question we are trying to answer – need to frame this well.
- Can't ignore the social determinants to health when making evaluations and recommendation.
- Need increasing focus on who is most vulnerable and how they are most impacted. Progress has been made over time but need to go further including understand the biases that underscore the decisions that are baked into risk assessments. Inequities are tacked on at the end, instead of integrated right from the start (see Susan Norris' presentation)
- Urgent need for assessment cannot be outweighed by a fuller need for data – delays have had a significant public health impact.
- Lessons learned from COVID pandemic – limited evidence promoting pharma interventions, considering exposure to air pollution impacting outcomes of COVID. Studies are ecological design, yet they are informing public health decisions. Mechanistic information and biological plausibility has been enough to drive public health interventions. Also, seeing inequities regarding co-exposures to air pollution, lack of access to health care, etc.
- Communication is really critical. Scientists are trained to question and probe – valuable for scientific progress, but not necessarily helpful for clear communication of the evidence.
- As science evolves and so will the recommendations.

Yukyan Lam report back
- Need to identify future and emerging hazardous agents.
  - Burden on industry to prove safety before market
- More focus on identifying relationships that are robust enough to support protective action.
  - Example of high risk of breast cancer in female border security guards
- Communication that just because it is on the market, doesn't mean it is safe.
- For new chemicals, need a more explicit way to trigger when those chemicals need to be incorporated into existing epi studies.
- For existing chemical pollutants, 'green taxes' can be used to incentivize exposure reductions and identifying no-regret substitutes.
- How do we study social determinants that can amplify the impact of hazardous agents
  - Community health surveys
  - Community input to prioritize chemicals, outcomes, output
  - Citizen science
  - More leveraging of existing evidence
  - For example, in land use decisions and other venues
  - We need two-way dialogue between community and scientists
- Important not to conflate equity and environmental justice (EJ) – they are much too important to get lost. Cumulative impacts analysis may be a better way to respond to concerns in EJ communities.
  - Let us be deliberate about the use of the term EJ, and incorporate it with equal deliberation

Marike Kolossa report back
- Communication
  - Necessary for transparency
  - Should be linked to regulation and policy, to better enable communities to respond
  - Communication should be part of the education training of students as they train in the field of EH

Jennifer Sass report back
- Distinction between early indicators, and substances about which we already know a lot. For substances with lots of data, evaluations are very slow.
- There is a conflict between thorough methods and timely response; when is an evaluation 'good enough' to support health-protective policies and actions:
  - If we do a 'fit for purpose' narrow or limited assessment, then we need to revisit it regularly, to update
  - Note that every health endpoint that is excluded, is a potential disease that is not investigated, minimized, and compensated
- Need more emphasis on addressing community concerns, worker concerns, etc.
- Could address chemicals by including p-chem characteristics as hazard endpoints – PFAS are being proposed to be addressed as a class, because they are extremely mobile and persistent.
- Health Canada is taking a public health approach to chemicals, starting with an illness or health outcome, and then go back to look at what chemicals may cause that health outcome. For example, contribution to CV disease from chemicals, pollution, gene-environment interactions. US EPA has a paper on merging and using epi and tox data.
  - Finland took on CV disease from all risk factors and dramatically cut cardiovascular disease
- Work that supports non-regulatory actions is very important, and can be done in a timelier way, including supporting communities, market transformations, worker health and safety.
- How can we expand and support (including with funding) more committees and decision-making bodies that include more representatives of EJ, fence-line and disproportionately burdened communities, and those health and environment perspectives? Are there examples that do this well? Help?
  - In the European Guidelines in Breast Cancer Screening and Prevention, one panel member was a cancer survivor, and president of advocacy group Europa Donna https://healthcare-quality.jrc.ec.europa.eu/
  - The National Health and Medical Research Council in Australia include stakeholders from community in their guideline development process, including on topics of lead and fluoride
  - In the WHO air quality guidelines, one of the GDG group members was for "Clean Air Asia", an international non-governmental organization that leads the regional mission for better air quality and healthier, more livable cities in Asia

Xenia Trier report back
- Expanding expertise
- Funding needs to be increased
- Need to strengthen independent research, expand fellowships.
- WHO and IARC are really critical contributors
- Focus on where the concern/impact is largest, to prioritize what to study
  - Who are the disproportionately impacted groups – could be occupational, community, age-related, cumulative factors, multiple stressors

- More work needs to be done with systematic review on what is known and what is not known (work on evidence maps by NTP OHAT, TEDX, IRIS and PRHE re v important to this process).
- Equity and EJ – those who are most harmed are often not those that decide what are the most relevant studies. Who has the power to choose the studies? They may not be connected to the communities most harmed. People in developing countries are not prioritized well.
- Co creation of Projects with EJ groups is critical – how do we do this in practice? We need to think about a global coalition and approach to regulation.
- Timeliness – evidence has to match the needs of the decision. If we want to act earlier, then we have to respond to weaker signals, less confidence in studies. See David Gee's Late Lessons, which showed via over 30 case studies that both exposures and harm expand over time with more research, and exposure limits always come down if based on the scientific evidence of harm. If we delay action, harm will expand, so good justification in taking early action. Decisions by classes of chemicals is a valid way to speed things up.
- Leverage points, places to intervene – most powerful way is to change the minds of those that make the decisions. Data is the least powerful way to change minds. Should we be working more with industry?
- Important to think about who benefits (global north) and who bears the burden (global south).
- California Proposition 65 – an public 'right to know' product labelling requirement - is a way of counting uncertainty against the product; incentivizing moving away from toxic ingredients

ABSTRACTS & BIOS

David Gee

David was educated in politics and economics at York University (1965-68) and has worked for over 40 years at the science/policy interface of occupational, public, and environmental risk assessment & reduction, with UK Trade Unions; with the UK Environmental Group, Friends of the Earth, where he was Director; and, from December 1995 to May 2013, with the European Environment Agency, an EU environmental information providing body in Copenhagen, where he was Senior Adviser, Science, Policy, Emerging Issues.

He has published reports and peer reviewed articles and lectured on Scientific Uncertainty; the Precautionary Principle; Environmental Health; Environmental Taxes and Ecological Tax Reform; Clean production; Eco-efficiency; Endocrine disrupting chemicals; Electro-magnetic fields; Evaluating evidence; and anticipatory research.

He is initiator, co-editor, and contributor to the widely cited and used EEA (European Environmental Agency) reports, "Late Lessons from Early Warnings: The Precautionary Principle 1898-2000" (2001), and "Late Lessons from Early Warnings: Science, Precaution, Innovation" (EEA, 2013).

He is now an Associate Fellow at the new Institute of Environment, Health, and Societies, at Brunel University, London.

Jennifer Sass

Jennifer Sass is a Senior Scientist at the Natural Resources Defense Council (since 2001), an environmental non-profit organization. She also holds a position as part-time faculty at George Washington University Milken School of Public Health (since 2008). Much of Dr Sass' work is focused on understanding and explaining the science behind toxic chemical regulation and on advocating for regulations that are consistent with science, health policy, and environmental law. She frequently provides testimony and scientific briefings for members of Congress and federal advisory committees. She has published over four dozen articles in peer-reviewed journals. She is a Board Member of the NIEHS National Toxicology Program Board of Scientific Counselors (since 2016). She holds BSc, MSc, and PhD (1998) degrees from the University of Saskatchewan, College of Medicine, Department of Anatomy and Cell Biology, and a Post-Doctoral Certificate (2000) from the University of Maryland, College of Medicine, Program in Human Health and the Environment.

Nicholas Chartres

Nicholas Chartres, PhD, is the Director of Science and Policy at UCSF's Program on Reproductive Health (PRHE) and the Environment and is focused on environmental health research translation methods and the promotion of evidence-based policies to prevent exposures to harmful environmental chemicals. In this role, he oversees the Navigation Guide Working Group, which is focused on increasing the knowledge and awareness of systematic review methods in environmental health and policy decision-making arenas. Dr. Chartres is an expert in the application of systematic review methods to observational studies in the public and environmental health fields. He conducted the first in-depth assessment of these methods used by national and international organizations during hazard identification and the risk assessment of environmental hazards. He has collaborated with international teams of researchers to evaluate the tools currently used to assess risk of bias in observational studies, which is central to the development of credible public health guidelines and environmental risk assessments. Dr. Chartres is also part of the World Health

Organization/International Labor Organization Joint Working Group on Occupational Health Systematic Review Methods, which aims to estimate the global burden of work-related disease and injury.

<u>Aditi Shah</u>

Aditi Shah is the Science Policy Analyst for PRHE's Science & Policy team. Aditi graduated from the University of California, Berkeley with her MPH in Global Health and Environment. She is particularly interested in the potential of using mapping and data visualization techniques to better inform environmental justice policies. Her previous research focused on identifying methodologies to map and link geographic entities with water contamination, demographic, and socioeconomic data. Prior to working at PRHE, Aditi worked at The Earth Institute, Tracking California, and The Parker Foundation.

<u>Day 1, Monday Feb 8th</u>

<u>Matthieu Schuler</u>

Matthew Schuler is the Managing General Director of the Science for expertise Department, and Head, Risk Assessment Division, ANSES, France. A graduate of the Ecole des Mines in 1993, and then of the Corps des Mines in 1996, Matthieu Schuler has devoted himself from the outset of his career to controlling risks, particularly those associated with radioactivity, from the facilities that generate them through to human health and environmental protection. Following several assignments in France and abroad, he joined the Nuclear Safety Authority (ASN) in 1996 as deputy head of the office for control of nuclear steam supply systems, before taking charge of this office in 1999.

In 2002, he became Deputy Director of the Ecole des Mines in Nantes, where he actively participated in managing the school, consolidating its laboratories' scientific partnerships, and expanding the international scope of the campus. At the same time, he held the position of Deputy Director at the Regional Directorate for Industry, Research and the Environment of the Pays de la Loire region.

In 2009, he joined the IRSN as Deputy Director of the Human Protection Department, before becoming the institute's Strategy Director in 2011.

<u>Mark Mitchell</u>

When science and policy fail high risk communities: a case study of hexavalent chromium

Bio

Mark Mitchell M.D., MPH, FACPM is Associate Professor of Climate Change, Energy, & Environmental Health Equity at George Mason University. He also co-chairs the National Medical Association's Commission on Environmental Health.

A preventive medicine physician trained in environmental health and health policy, Dr. Mitchell has spent over twenty years working in the public health sector, including as Director of the Hartford, Connecticut Health Department. He spent fifteen years working with environmental justice communities to prevent and reduce environmentally related disease as well as to change policies that are detrimental to environmental health. He is the Founder and Senior Policy Director of the Connecticut Coalition for Environmental Justice.

Dr. Mitchell earned his medical degree from the University of Missouri-Kansas City and his Master of Public Health from The Johns Hopkins University.

Abstract

This is a case study of a release of chromium VI from a brownfields site a high-risk neighborhood in Hartford, Connecticut, USA. We will discuss how government scientists and health experts handled uncertainty, community relations, communications and reliance on inadequate science, as well as community knowledge and perceptions of the event and government scientists.   The purpose of this opening session is to focus further discussions around how scientific uncertainty and communications affected communities such as this one and the need to improve the protection of vulnerable communities from chemical exposures.

Patrick Breysse

Overcoming complexity and establishing causality in ATSDR investigations

Abstract

The Agency for Toxic Substances and Disease Registry (ATSDR) was created by the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) of 1980 to serve as a science-based public health agency working to address community concerns about hazardous waste. For three decades, ATSDR has protected people from environmental hazards in more than 6,000 U.S. communities. Along with Atlanta-based headquarters staff, ATSDR staff in 10 regional offices support more than 400 experts in Environmental Health across the country, who are ready 24/7 to respond to environmental health threats, such as natural disasters and chemical spills. This presentation addresses the evidence-based practices that ATSDR uses to overcome complexity and uncertainties in establishing causality. Two case examples are highlighted: (1) ATSDR's exposure assessments for PFAS (Per-and Polyfluoroalkyl substances) and (2) ATSDR's assessment of evidence supporting causality for adverse health effects from exposures to drinking water contaminants (e.g., trichloroethylene, perchloroethylene vinyl chloride, and benzene) at Camp Lejeune Marine Corps Base in North Carolina. ATSDR is engaged in PFAS activities across the country to determine where and how exposures are occurring, to understand the relationship between PFAS exposure and the risk of health effects, and to identify and implement strategies to prevent exposure in the future. As the science of PFAS rapidly evolves, ATSDR has been challenged in adequately answering community concerns with respect to whether their level of PFAS exposure is concerning and the potential health effects associated with this exposure.

Bio

Pat Breysse, PhD, joined the Centers for Disease Control and Prevention (CDC) in December 2014 as the Director of NCEH/ATSDR. Dr. Breysse leads CDC's efforts to investigate the relationship between environmental factors and health. He came to CDC from the Johns Hopkins University where his research focused on the evaluation and control of chemical, biological, and physical factors that can affect health, with a particular concentration on risk and exposure assessment. Under Dr. Breysse's leadership, the agency has prioritized work on exposure to lead, safe drinking water, initiated new ATSDR actions to address exposure to hazardous chemicals, and has played a critical role in CDC's emergency preparedness and response to natural disasters and chemical exposures.

Dr. Breysse received his PhD in Environmental Health Engineering from Johns Hopkins University in 1985 and completed postdoctoral training at the British Institute for Occupational Medicine in Edinburgh, Scotland.

Christopher Portier

Decision-making under uncertainty and ignorance

Abstract

This brief introduction will characterize several different types of uncertainty and ignorance that can impact decision-making. The linkage between uncertainty, ignorance, transparency, and trust will also be discussed. Some of the methods by which decision-makers try to reduce the impacts of uncertainty and ignorance will be discussed and examples of failures to implement these methods will be used to illustrate their impacts on a final decision. Suggestions for reducing the impacts of uncertainty and ignorance on the trust and transparency of decisions are provided.

Bio

Prof. Dr. Christopher J. Portier is a semi-retired expert in the design, analysis, and interpretation of environmental health data with a focus on carcinogenicity. Dr. Portier is currently a Senior Collaborating Scientist (part-time) with the Environmental Defense Fund, and an Adjunct Professor at Emory University and Maastricht University. He is also working with several governments on risk assessment issues and is a consultant on chemical-related issues (including glyphosate) to several US law firms.

He has authored more than 200 peer-reviewed publications and book chapters. During his 36+ years of research, Dr. Portier has focused on using systems-based approaches to understand the impact of the environment on human health. He has received numerous awards including the President's Dream Green Team Award from President Obama, the Spiegelman Award from the American Public Health Association, and the Outstanding Practitioner of the Year Award from the International Society for Risk Analysis. He is an elected Fellow of the International Statistics Institute, the World Innovation Foundation, the American Statistical Association, and the Collegium Ramazzini.

Prior to his retirement, Dr. Portier served as the Director of the US National Center for Environmental Health at the Centers for Disease Control and Prevention and Director of the Agency for Toxic Substances and Disease Registry. Prior to this, Dr. Portier was at the US National Institute of Environmental Health Sciences (NIEHS) where he conducted research on environmental health and served as the Director of the Environmental Toxicology Program, the Associate Director of the National Toxicology Program, and the Senior Scientific Advisor to the Director of NIEHS.

Day 2, Tues Feb 9th

Michael Kundi

Bio

Michael Kundi studied Psychology, Medicine and Mathematics at the University of Vienna and got his PhD at the University of Vienna in 1979 and obtained his habilitation in Epidemiology and Occupational Health from the Medical University of Vienna in 1989. He is since 2004 head of the Institute of Environmental Health of the Medical University of Vienna. His research covers the full range of epidemiological, clinical, field and laboratory experimental studies of environmental and occupational factors. He has published about 200 articles in peer-reviewed journals. Main research interests in the past years are health effects of particulate matter, indoor pollutants, and electromagnetic fields.

James Lin

Some key differences in the ICNIRP and IARC evaluations of RF evidence

Bio

James C. Lin is a professor of bioengineering and electrical engineering at the University of Illinois-Chicago. At the University of Illinois, Lin has served as head of the Bioengineering Department, Director of the Robotics and Automation Laboratory, and Director of Special Projects in the College

of Engineering. He also held an appointment as the NSC Research Chair from 1993-1997. Lin is the author of more than 140 journal papers, and author or editor of seven books. After beginning his higher education at Whitworth College in Spokane, Wash., he received the BS, MS and PhD (1971) degrees in electrical engineering from the University of Washington, Seattle. Lin's academic career took him from teaching and research in Seattle, on to positions at Wayne State University in Detroit and finally at the University of Illinois-Chicago, where he has served as a professor of electrical engineering, bioengineering and physiology and biophysics since 1980. Professor Lin's research interests include: Biomedical instrumentation; Electromagnetic Engineering for Biology and Medicine; Imaging and Sensing; Bioelectromagnetics; Mobile Telecommunication Safety; Biological Interactions of Electromagnetic Radiation Including RF (Radio Frequency), Microwaves, and Lasers.

Roy Harrison

Divergent evaluations on NO2 toxicity: COMEAP report on quantification of all-cause mortality based on associations with long-term average NO2 concentrations

Abstract

(see abstract presentation with Alison Gowers, below)

Bio

Roy Harrison is Queen Elizabeth II Birmingham Centenary Professor of Environmental Health at the University of Birmingham, UK, and Distinguished Adjunct Professor at King Abdulaziz University, Saudi Arabia. His research interests are in air pollution, especially airborne particulate matter. He has also been heavily engaged at the science/policy interface as a member of several government technical advisory groups for the Department of Health and the Department for Environment, Food and Rural Affairs (Defra) in the U.K. including past membership of Defra's Science Advisory Council. He was a contributor to the World Health Organization Global Air Quality Guidelines and the Guidelines for Quality of Indoor Air. He was appointed an Officer of the Order of the British Empire (OBE) in the 2004 New Year Honours List and elected a Fellow of the Royal Society in 2017. He is author of almost 600 papers in the peer-reviewed literature and is listed by Web of Science as a Highly Cited Researcher.

Alison Gowers

Divergent evaluations on NO2 toxicity: COMEAP report on quantification of all-cause mortality based on associations with long-term average NO2 concentrations

Abstract

NO_2 Because air pollutants such as nitrogen dioxide (NO2) and particles are emitted from the same sources, their concentrations in outdoor air are often highly correlated. This has made it difficult to assess whether ambient concentrations of NO2 have direct adverse effects on health (HPA, 2011)[1]. Nonetheless, epidemiological studies report associations of NO2 with increased mortality risk and other health outcomes, and the evidence to support some direct effects of NO2 has grown in recent years (e.g. WHO, 2013;[2] COMEAP 2015[3]). Considering this, the UK's expert advisory Committee on the Medical Effects of Air Pollutants (COMEAP) was asked to provide advice on quantifying the mortality effects associated with long-term average concentrations of nitrogen dioxide (NO2). Given the uncertainties in the available evidence, and the limitations of available methods to ascribe causality of reported associations to individual pollutants, an expert judgement approach was used to develop recommendations for quantification methods. The majority of committee members supported the proposed approaches. However, some members dissented because they considered

that the uncertainties meant that providing quantitative advice was inappropriate. Both the majority and dissenting views are detailed in COMEAP's report (COMEAP, 2018).[4]

[1] Nitrogen dioxide: workshop for research on the health effects - GOV.UK (www.gov.uk)

[2] WHO/Europe | Air quality - Review of evidence on health aspects of air pollution – REVIHAAP project: final technical report

[3] Nitrogen dioxide: health effects of exposure - GOV.UK (www.gov.uk)

[4] Nitrogen dioxide: effects on mortality - GOV.UK (www.gov.uk)

Bio

Alison has an MSc in Toxicology from Surrey University and has undertaken hazard characterization and risk assessment of chemical contaminants in the environment within both consultancy and government departments/agencies. For the last 10 years she has worked for Public Health England (and its predecessor, the Health Protection Agency) on air quality and public health. Alison leads the Scientific Secretariat which supports the work of the UK's independent expert advisory Committee on the Medical Effects of Air Pollutants (COMEAP). Much of her work with the committee has been concerned with quantifying health effects which are associated with air pollution.

Linda Birnbaum

Different strengths of timely evidence needed in divergent social and political contexts: various case studies

Bio

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S. is the former Director of the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, and the National Toxicology Program (NTP). After retirement, she was granted scientist emeritus status and still maintains a laboratory. As a board-certified toxicologist, Birnbaum served as a federal scientist for 40 years. Prior to her appointment as NIEHS and NTP Director in 2009, she spent 19 years at the U.S. Environmental Protection Agency (EPA), where she directed the largest division focusing on environmental health research.

Birnbaum has received many awards and recognitions. In 2016, she was awarded the North Carolina Award in Science. She was elected to the Institute of Medicine of the National Academies, one of the highest honors in the fields of medicine and health. She was also elected to the Collegium Ramazzini, an independent, international academy comprised of internationally renowned experts in the fields of occupational and environmental health and received an honorary Doctor of Science from the University of Rochester and a Distinguished Alumna Award from the University of Illinois. She has also received Honorary Doctorates from Ben-Gurion University, Israel, and Amity University, India; the Surgeon General's Medallion 2014; and 14 Scientific and Technological Achievement Awards, which reflect the recommendations of EPA's external Science Advisory Board, for specific publications.

Birnbaum is an active member of the scientific community. She was vice president of the International Union of Toxicology, the umbrella organization for toxicology societies in more than 50 countries, and former president of the Society of Toxicology, the largest professional organization of toxicologists in the world. She is the author of more than 1000 peer-reviewed publications, book chapters, abstracts, and reports. Birnbaum's own research focuses on the pharmacokinetic behavior of environmental chemicals, mechanisms of action of toxicants including endocrine disruption, and linking of real-world exposures to health effects. She is an adjunct professor in the Gillings School of Global Public Health, the Curriculum in Toxicology, and the Department of Environmental Sciences and Engineering at the University of North Carolina at Chapel Hill, as well as in the Integrated Toxicology and Environmental Health Program at Duke University where she is also a Scholar in Residence.

A native of New Jersey, Birnbaum received her M.S. and Ph.D. in microbiology from the University of Illinois at Urbana-Champaign.

Theo Vermeire

Core beliefs, weights of evidence and handling uncertainties in risk assessment – PFOA case study

Abstract

Reasoning in the interpretation of scientific evidence with respect to the risk of adverse health effects in the human population is deeply rooted in (different) scientific paradigms and in differences in context: e.g., toxicologists are mostly oriented toward ex ante (regulatory) health protection, while the epidemiologists are oriented toward ex post public health risk reduction. Moreover, while science is often seen as 'value free', universal and independent, quite often scientific controversies about environmental health issues are convoluted by (implicit and hidden) core beliefs and normative value judgements from experts and by their professional paradigms. From argumentation analysis of controversial scientific positions on endocrine disruptive compounds, we have identified the structure of argumentation and five main standpoints. We observed that the differences in the main standpoints differed in the nature of the disagreement; some were disagreement on interpretation of science (interpretative ambiguity), while others differed in normative valuation (normative ambiguity). To assess to what degree and how the professional and contextual differences between disciplines affect the evaluation of a specific substance we evaluated argumentation in four risk assessments of PFOA (RIVM, UBA, US-EPA, EFSA (European Food Safety Authority)) applying the rules of pragma-dialectic argumentation theory. Aspects considered were sources of evidence used and reasons to include or exclude evidence, what key evidence weakened or strengthened the weight of evidence on causality, what ancillary evidence was used and how weight of evidence was phrased or categorized. The generic and PFOA/PFAS specific results from the evaluation were presented with reflections on causal reasoning in the context of establishing the weight of evidence in risk assessment. It is recommended that all lines of evidence in exposure, hazard and risk assessment should be weighed individually and taken all together for a conclusion on causal relations, applying weight-of-evidence criteria with clear and transparent documentation and argumentation.

Bio

Theo Vermeire, PhD, is a registered toxicologist and currently working as senior scientist at the Centre for the safety of Substances and Products of the National Institute for Public Health and the Environment in the Netherlands (RIVM), where he has served in a sizable number of scientific and managerial positions. He studied (biochemistry at the University of Utrecht and agricultural chemistry at the University of Wageningen and obtained a PhD in risk assessment from the University of Utrecht. His main interests are with the science-policy interface, regulatory risk assessment, alternatives for animal testing and development of risk assessment tools specifically for exposure assessment, uncertainty analysis and weight-of-evidence approaches in hazard and risk assessment.

He has been involved in many advisory bodies and expert groups developing guidance and tools for risk assessment, *e.g.,* for IPCS/WHO, EU, OECD, EEA. Currently he is chair of the Scientific Committee for Health, Environmental and Emerging Risks (SCHEER), one of the non-food Scientific Committees of the European Commission.

Elisabeth Cardis

Bio

Elisabeth Cardis is Research Professor in Radiation Epidemiology at ISGlobal. Before moving to CREAL (now ISGlobal Campus MAR) in April 2008, she was the head of the Radiation Group at IARC in Lyon, where she coordinated studies of ionising and non-ionising radiation for over 20 years. She was a visiting scientist at the Radiation Effects Research Foundation in Hiroshima, Japan, in 1981-2 and received a PhD in Biostatistics from the School of Public Health of the University of Washington in Seattle, in 1985.She is the author of over 100 indexed publications. She is a member of the board of the MELODI (Multidisciplinary European Low Dose Initiative) platform and is on the advisory board of the Israeli Information Centre for Non-Ionising Radiation and member of the radiofrequency working group of the French Agency for Food, Environmental and Occupational Health & Safety (which she chaired until 2013). She is an affiliate of the R. Samuel McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Canada. She chaired the IARC Monographs working group on Ionising Radiation and UV and was member of the High Level Expert Group on European Low Dose Risk Research, of the Steering Committee for the Swiss National Non-Ionising Radiation Programme, the Spanish Evaluation Committee on Radiofrequency and Health, the US National Academy of Sciences BEIR VII Committee, of the Expert Group on Health for the UN Chernobyl Forum and of the project management board of EMF-Net, the steering committee of the EU funded EFHRAN project (EMF risk assessment coordination network), the scientific advisory board of the WHO International EMF project and a corresponding member of ICNIRP and consultant to the United Nations Scientific Committee on the Effects of Atomic Radiation.

Day 3, Wed Feb 10th

Bjorn Hansen

Bio

Bjorn Hansen is ECHA's second Executive Director with a mandate running from 1 January 2018 to 31 December 2022. He is ECHA's legal representative, in charge of the day-to-day management and all staff matters.

After a post-doc in probability theory in Germany, he joined the European Commissions in 1991. Working first at the European Chemicals Bureau at the Joint Research Centre in Italy and then from 2003 in the Chemicals Unit of DG Environment in Belgium. There, Bjorn became Head of Unit in 2012. He already spent one year in ECHA in 2007-2008 as Director of Operations.

Bjorn was involved in developing REACH and CLP from their very early days. He has been involved in international chemicals work since 1991.

Kurt Straif

IARC – evidence evaluation and integration: the case of Glyphosate

Abstract

Glyphosate is just one of more than a thousand agents that has been evaluated and classified regarding its potential cancer hazard by the IARC Monographs Programme. About one half of all agents have been classified into a Group 2B (possibly carcinogenic to humans) or higher, and more than 200 agents have been classified - like glyphosate - into Group 2A (probably carcinogenic to humans) or higher. Nevertheless, the systematic review, evidence synthesis, evaluation, and classification of the published scientific literature on glyphosate has probably received more (and lasting) attention than the classifications of Radiofrequency EMF (Group 2B), Formaldehyde, Diesel

engine exhaust, Processed meat and Contraceptives and combined estrogen–progestogen menopausal therapy (Group 1), altogether.

This presentation will start with a concise summary how glyphosate was evaluated by evidence stream and overall, in line with the Preamble to the IARC Monographs Programme. Next, it will explore what has *not* contributed (despite various claims) and what may have contributed to divergent evaluations of glyphosate by various agencies. In preparation for the breakout discussion, and drawing from experience with other systematic reviews, broader issues possibly contributing to divergent evaluations will be explored with the aim to contribute towards principles of transparent and consistent systematic review processes in hazard and risk assessments.

Bio

Kurt Straif was long-term Head of the Section of Evidence Synthesis and Classification at the International Agency for Research on Cancer, WHO, Lyon, France, where he directed the programs of the IARC Monographs, the IARC Handbooks of Cancer Prevention and the WHO Classification of Tumours. He is now an Associate Researcher at ISGlobal, Barcelona, Spain, and a Visiting Professor at Boston College.

He has co-authored more than 200 scientific papers and was Editor and Associate editor of several books (including The World Cancer Report; Air pollution and Cancer; Social Inequalities in Cancer) and has received the Champion of Environmental Health Research Award of the US NIEHS (2016), the Distinguished Lecture in Occupational and Environmental Cancer of the U.S. NCI (2018), and the ISEE Research Integrity Award (2019).

He studied Medicine, Epidemiology, Public Health, and Philosophy in Europe and the United States and is Board-certified in Internal Medicine and in Occupational, Environmental and Social Medicine.

Xenia Trier

Governing complex risks when evidence is limited – from SOER2020 to the EU chemicals strategy for sustainability

Bio

Xenia Trier is an expert on chemicals, environment, and health at the European Environment Agency. Xenia Trier has worked at the EEA since 2016, linking science to policy and in collaboration with the EU agencies ECHA and EFSA, to provide evidence-based advice on the risk governance of chemicals to EU policy makers. Current topics range from emerging risks and their detection, very persistent chemicals (including PFAS), mixtures, grouping, human biomonitoring, indicators and to innovation in chemicals and products that are safe-and-circular-by-design – with the aim to support a transition to a circular and non-toxic economy. Prior her work at the EEA, she worked 20 years as a researcher and advisor to the Danish Food and Environment Authorities, the Nordic Council of Ministers and EU on analysis and risk assessment of chemicals in food contact materials. Her experience on PFAS includes their uses, characteristics, toxicities and analyses in air, water, materials, food and blood, part of which was done during her PhD studies on PFAS in food contact materials (2007-2011). Subsequently she led four PFAS enforcement campaigns in Denmark and Norway and supported the Danish Food Authorities in the development of a recommendation for a Total organic fluorine limit in food paper packaging, to achieve cleaner materials. The work included support to businesses in setting procurement criteria for PFAS-free materials. Over the years, Xenia Trier has developed a wide network of scientists, agencies, policy makers, NGOs, and business, which supports the sharing of knowledge of PFAS. Xenia lives in Copenhagen, Denmark.

Anna Beronius

Evaluating EDCs systematically: the SYRINA approach

Abstract

Endocrine disruptors (EDs) are exogenous substances that interfere with the normal function of the hormone system and may cause serious health effects, such as neurodevelopmental, reproductive, and metabolic disorders and cancers. Exposure to EDs during early development, e.g., in fetal life and small children, specifically raises concern since endogenous hormone signaling plays a critical role in organ system development. Minimizing potential human health risks from EDs has for several years been a highly prioritized issue for chemicals regulation globally, but identification and assessment of EDs has proven complex and sometimes controversial. This is partly due to the complex toxicity of EDs and that standardized toxicity tests, which are commonly required for regulatory hazard and risk assessment of chemicals, have been inadequate for identifying sensitive effects caused by endocrine disruption. Consequently, it is important that all available relevant data are considered in an objective, structured and transparent manner when assessing ED properties of chemicals. The framework for Systematic Review and Integrated Assessment (SYRINA) of EDs was proposed in 2016 based on a series of workshops including researchers and other experts from universities and organizations in Europe, the US and Australia (Vandenberg et al. 2016). The SYRINA was based on systematic review methodology and specific approaches developed in the field of environmental health and for assessing health risks of chemicals. It provides a structured approach to identifying, evaluating, and integrating different types of data (human, wildlife, laboratory animal, *in vitro* and *in silico*) to answer the question whether a specific substance is an ED. This presentation will address advantages and challenges to applying systematic review methodology in the assessment of EDs, describe the SYRINA framework, and discuss this approach in the context of identifying EDs in the regulatory setting.

Vandenberg LN, Ågerstrand M, Beronius A, Beausoleil C, Bergman Å, Bero LA, Bornehag C-G, Boyer CS, Cooper GS, Cotgreave I, Gee D, Grandjean P, Guyton KZ, Hass U, Heindel JJ, Jobling S, Kidd KA, Kortenkamp A, Macleod MR, Martin O, Norinder U, Scheringer M, Thayer KA, Toppari J, Whaley P, Woodruff TJ, Rudén C. 2016. "A proposed framework for the systematic review and integrated assessment (SYRINA) of endocrine disrupting chemicals." Environmental Health 15:74.

Bio

Dr Anna Beronius is a toxicologist and Assistant Professor at the Institute of Environmental Medicine, Karolinska Institutet, in Sweden. Dr Beronius conducts research in regulatory toxicology, with a focus on minimizing risks to human health from endocrine disrupting chemicals and chemical mixtures. She has a specific interest in methodologies that promote structure and transparency in hazard and risk assessment of chemicals, such as weight of evidence assessment, systematic review methodologies and adverse outcome pathways (AOP). Currently, her research is specifically focused on facilitating structured use of mechanistic understanding and data in assessments of endocrine disruptors. She is one of the initiators and developers of the Science in Risk Assessment and Policy (SciRAP) web-based platform (www.scirap.org) and was one of the coordinators of the international project to develop the SYRINA (Systematic Review and Integrated Assessment) framework for endocrine disruptors. Dr Beronius is also involved in various expert assignments to support national and international agencies and organisations in hazard and risk assessment. She teaches at Karolinska Institutet and other institutions on the topics of endocrine disrupting chemicals and risk assessment methodologies and is involved in organizing courses in health risk assessment, for example at Karolinska Institutet and at the European Food Safety Authority.

Tracey Woodruff

Towards transparent and consistent Systematic Review Processes in Hazard and Risk Assessments?

Abstract

Systematic review (SR) methods are increasingly being recommended and used to inform environmental health decisions. Use of SR has direct, long-term effects on public health, due to improved consistency of evidence review with lower bias. Systematic reviews have been adapted from clinical medicine, where data is largely from randomized, controlled trials. Environmental health SRs often rely on data from human epidemiological studies to inform the relationship between exposures and adverse health outcomes. To bridge between SR in environmental health and the clinical sciences, authoritative bodies, U.S. agencies, and academic scientists developed and implemented validated, peer-reviewed SR methods including the Navigation Guide and the U.S. National Toxicology Program's OHAT. These methods use widely accepted empirically based approaches to evaluate human epidemiological evidence. In contrast, US EPA under the Toxic Substances Control Act (TSCA) is using a significantly different approach, with major implications for regulation of hazardous chemicals and public health. While there has been an increase in SR use in environmental health over the last decade, there is divergent approaches to key elements of the SR process, in particular assessing the risk of bias in observational design studies, evaluation of the quality of the body of evidence and integration with other streams of evidence. Areas of concern for risk of bias include use of quantitative scoring methods, an overall risk of bias rating for a study, and exclusion of studies based on one 'critically deficient' domain. When evaluating the quality of a body of evidence and synthesizing evidence into normative guidance, approaches in environmental health have adopted elements of GRADE (Grading of Recommendations Assessment, Development and Evaluation). However, there is still discussion about accounting for observational human studies and how to assess magnitude of effect. Finally, approaches vary in how to integrate with other streams of evidence such as nonhuman studies. We will discuss US EPA's current approach in conducting chemical risk evaluations in comparison to the use of validated, best practice methods to assess human epidemiological evidence by international authoritative bodies and how it has led to divergent evaluations of the evidence.

Bio

Tracey Woodruff, PhD, MPH is the Director of and Alison S. Carlson Endowed Professor for the Program on Reproductive Health and the Environment (PRHE) and is a Professor in the UCSF Department of Obstetrics, Gynecology and Reproductive Sciences and the Philip R. Lee Institute for Health Policy Studies. She is also the Director of a newly awarded NIEHS Environmental Health Core Center grant, the Environmental Research and Translation for Health (EaRTH) Center at UCSF. She is a recognized expert on environmental pollution exposures and impacts on health, with a focus on pregnancy, infancy and childhood, and her innovations in translating and communicating scientific findings for clinical and policy audiences. She has authored numerous scientific publications and book chapters, and has been quoted widely in the press, including USA Today, the San Francisco Chronicle and The New York Times. Before joining UCSF, Dr. Woodruff was a senior scientist and policy advisor for the U.S. EPA's Office of Policy. She was appointed by the governor of California in 2012 to the Science Advisory Board of the Developmental and Reproductive Toxicant (DART) Identification Committee.

Erik Millstone

Bio

Erik Millstone is an Emeritus Professor of Science Policy at the University of Sussex. He has been researching the causes and consequences of innovation and technological change in the agricultural

and food sectors since the mid-1970s. He has also analyzed the structures and operations of the regulatory institutions responsible for agricultural and food policies, especially safety standards. Much of his research has focused on locating and revealing the interactions between scientific and political considerations, and on the conditions under which science-based regulatory policy-making can achieve and reconcile both scientific and political legitimacy. As a public intellectual, he has frequently argued in favor of reforming those institutions and their policies to better protect public and environmental health.

Vince Cogliano

Bio

Dr Cogliano is the deputy director for scientific programs at the Office of Environmental Health Hazard Assessment at the California Environmental Protection Agency. The office protects and enhances the health of Californians and the state's environment through scientific evaluations that inform, support, and guide regulatory and other actions.

Previously, at the U.S. Environmental Protection Agency, Dr Cogliano served as director of the Integrated Risk Information System program and as deputy to the agency's scientific integrity official.

Dr Cogliano also was head of the *IARC Monographs* program at the International Agency for Research on Cancer (part of the World Health Organization) in Lyon, France. The *IARC Monographs* are a series of scientific reviews that identify environmental factors that can increase the risk of human cancer.

Dr Cogliano received his PhD from Cornell University. Professional interests include qualitative and quantitative health risk assessment and its application to the protection of public health.

Day 4, Thurs Feb 11th

Kathryn Guyton

The key characteristics of carcinogens – IARC perspective

Abstract

The concept of 'key characteristics', properties of chemicals and other agents that confer potential hazard, was first developed for carcinogens and was based on properties of known human carcinogens as classified by the International Agency for Research on Cancer (IARC) (Smith et al., 2016; IARC, 2019; Smith et al., 2020). These key characteristics of carcinogens (KCs) have been applied in the evaluation of more than 70 diverse carcinogens at IARC (Guyton et al., 2018) and are now used as the basis for the evaluation of mechanistic data by the *Monographs* (2019 Preamble, Samet et al., 2019). This presentation will introduce the KCs approach and summarize its application in IARC *Monographs* classifications.

Bio

Dr. Kate Guyton is a Senior Toxicologist at the International Agency for Research on Cancer (IARC), World Health Organization in Lyon, France. Her prior work includes service as a Toxicologist at the US Environmental Protection Agency (2005-2014). As the Director of Scientific Affairs at CCS Associates (1998-2005), she worked with the US National Cancer Institute. Dr. Guyton received her BA (cum laude) and PhD from Johns Hopkins, with postdoctoral training at the US National Institutes of Health. Dr. Guyton has been certified as a Diplomate of the American Board of Toxicology since 1998.

Kristi Pullen-Fedinick

Application of high throughput data in regulatory decision-making – NGO perspective

Abstract

The process of evaluating chemicals in the environment for possible harms to people, wildlife, and ecosystems has been rapidly evolving over the last 10 years. Advances in computational biology, systems biology, high-throughput testing methodologies, exposure science and other areas have increased the capacity of agencies, academics, and regulated communities to generate information about many chemicals.

Amendments to the Toxic Substances Control Act (TSCA) in 2016 brought alternative test methods and strategies more affirmatively into regulatory practice in the United States by encouraging the US Environmental Protection Agency to reduce, refine, and replace, to the extent practicable, whole animal tests in toxicity testing. Other federal and state agencies have also been key players in developing methods for the rapid assessment of chemicals using non-animal methods.

While new tools and approaches have increased the ability to rapidly identify hazards and risk posed by chemicals in the environment, to be truly protective, the tools must be applied in ways that take disparate and disproportionate burdens into account. This presentation will focus on the strengths and limitations of emerging technologies when considering implications for environmental justice.

Bio

Kristi Pullen Fedinick, Ph.D., is the Director of Science and Data and a Senior Scientist in the People and Communities Program at the Natural Resources Defense Council. She also serves as an adjunct faculty member in the Department of Environmental and Occupational Health of the Milken Institute School of Public Health at The George Washington University. Dr. Pullen Fedinick's expertise spans environmental health and policy; molecular, structural, and computational biology; biochemistry; and the social determinants of health.

Dr. Pullen Fedinick's current work focuses on the use of scientific tools and methods to inform and shape policies and narratives centered on chemical exposures in marginalized communities. She utilizes geospatial and statistical tools to assess the geographic distribution of chemicals in the environment, with a particular emphasis on drinking water. Her work also includes the evaluation of high-throughput technologies, predictive toxicology, and computational approaches for use in chemical evaluations.

Dr. Pullen Fedinick has served on several committees of the National Academies, including the Committee on the Application of Systematic Review in TSCA Risk Evaluations, the Committee on Incorporating 21st Century Science in Risk-Based Evaluations, and the Standing Committee for Emerging Science for Environmental Health Decisions. She has also participated in multiple government, academic, and professional society panels and committees.

Marike Kolossa-Gehring

Use of Biomonitoring data in hazard and risk assessment of PFCs

Abstract

Use of Biomonitoring data in hazard and risk assessment of PFCs
Marike Kolossa-Gehring, André Conrad, Enrico Rucic, Aline Murawski, Rosa Lange, Anja Duffek, Jörg Wellmitz, Till Weber
German Environment Agency (Umweltbundesamt), Berlin/Dessau-Roßlau, Germany

Background and Methods - The European Food Safety Authority expressed the concern in its scientific opinion on the risk to human health related to the presence of perfluoroalkyl substances in food that parts of the European population might exceed the new TWI for the sum of four PFASs (PFOA, PFNA, PFHxS and PFOS). As the extent of the German population's internal exposure to perfluorinated alkylated substances (PFAS) and the risk associated with this exposure was unknown, time trends of PFAS exposure were investigated in samples from young adults of the German Environmental Specimen Bank (ESB) and exposure distributions in the population representative German Environmental Survey on children and adolescents (GerES V, 2014 to 2017). GerES V was jointly conducted with Wave 2 of the German Health Interview and Examination Survey for Children and Adolescents (KiGGS W2) of the Robert Koch Institute (RKI).
While the time trend was investigated in two consecutive studies in a total of 358 samples of the ESB from the years 1982 to 2019, in GerES V a sub-sample of 1,109 children and adolescents (3-17 years) was investigated. PFAS have been analyzed in blood plasma by UHPLC-HRMS and LC-MS/MS. Limits of quantification (LOQ) ranged from 0.25 to 1 µg/L, respectively. Standardized interviews i. a. on exposure relevant behaviors and living conditions were carried out with participants or their parents. For GerES socio-demographical data was used in statistical analyses.

Results - Declining temporal trends were observed for all PFAS (PFOA, PFNA, PFHxS, and PFOS) frequently detected in the ESB samples. The two legacy substances PFOA and PFOS were detected in every sample of the 2009–2019 dataset and showed the highest concentrations with ranges of 0.27–14.0 ng/ml and 1.21–14.1 ng/ml, respectively. High detection frequencies of 95% and 82% were also found for PFHxS and PFNA, respectively, but in lower concentrations (PFHxS: <LOQ – 4.62 ng/ml; PFNA: <LOQ – 3.66 ng/ml) than PFOA and PFOS.

Although these data show a clear decrease of exposure over the years, in current samples still 45% of concentrations of PFOA exceed the toxicologically derived health-based guidance value (HBM-I) of 2 ng PFOA /ml. In current ESB samples the HBM-I value for PFOS (5 ng/ml) and the HBM-II values (5 ng PFOA/ml and 10 ng PFOS/ mL for women in childbearing age and 10 µg PFOA /l and 20µg PFOS / l for the general population) were not exceeded. In the GerES V samples of children and adolescents for PFOA, PFOS and PFHxS 74% - 100% of measurements were at or above LOQ. For the other PFAS this fraction is 10% or less. Overall geometric mean (GM) concentrations were PFOA: 1.12 µg/l, PFOS: 2.49 µg/l, and PFHxS: 0.36 µg/l. For all three compounds, GMs are significantly higher in male participants and increase with socio-economic status and breastfeeding. For PFOA and PFOS, HBM-I value is exceeded by 21% and 7% of the participants, respectively. 0.2% of participants PFOS concentrations were even at or above the HBM-II value. Females older than 14 years exceeded the HBM-II value (10 ng PFOS/ml) PFOS by 0,23%, but not for PFOA (5 ng PFOA/ml) above which health impacts might occur.

Discussion - While the ESB shows a decline in PFAS exposure in young adults, GerES V provides population-representative data on German children's and adolescents' PFAS exposure. For a considerable fraction of the young generation, PFOS and PFOA exposure raises concern, as health effects can – according to current knowledge – not be ruled out with sufficient certainty. These data confirm the EFSA evaluation and show that a considerable risk derives from the PFAS exposure. Further data analysis and the new data from the European Joint Programme HBM4EU will provide an empirical basis for exposure reduction strategies and targeted risk communication.

Bio

Dr. Marike Kolossa-Gehring is a biologist and toxicologist and got her PhD from the Christian-Albrechts-University Kiel, Germany. Her research focuses on toxicology and human biomonitoring (HBM). She joined the German Environment Agency (UBA) in 1992 where she worked on environmental impacts on human health, general and international affairs of environmental chemicals regulation, toxicology and as head of the section "Pharmaceuticals, Washing- and Cleansing Agents".

She is Head of Section "Toxicology, Health-related Environmental Monitoring" and coordinator of the European Joint Programme HBM4EU, a joint effort of more than 120 partners from 30 countries, the European Environment Agency and the European Commission, co-funded under Horizon 2020. At the UBA she is in charge of managing the German Federal Human Biomonitoring Program consisting of German Environmental Survey (GerES), the part on human samples of the German Environmental Specimen Bank (ESB), the German Human Biomonitoring Commission, and the HBM cooperation between the German Chemical Industry Association (VCI) and the Federal Ministry for the Environment, Nature Conservation, and Nuclear Safety (BMU).

She was involved in the development of assessment strategies and guidelines at the national, EU and OECD level, vice-chair and chair of the OECD Endocrine Disruptor Testing and Assessment Task Force from 2006 to 2010. She was Work Package Leader in the EU HBM projects ESBIO, DEMOCOPHES and COPHES, the Consortium to Perform Human Biomonitoring on a European Scale preparing and piloting a European human biomonitoring study. From 2011 to 2014 she was Governmental Councillor of the International Society of Exposure Science (ISES).

Martyn Smith

Future applications of key characteristics approaches

Abstract

The concept of 'key characteristics', properties of chemicals and other agents that confer potential hazard, was first developed for carcinogens and was based on properties of known human carcinogens as classified by the International Agency for Research on Cancer (IARC) (Smith et al., 2016; IARC, 2019; Smith et al., 2020). These key characteristics of carcinogens were applied in the evaluation of diverse carcinogens (Guyton et al., 2018) are now used as the basis for the evaluation of mechanistic data at IARC (2019 Preamble, Samet et al., 2019). They are also widely used by authoritative bodies and regulatory agencies, such as the National Toxicology Program Report on Carcinogens (Atwood et al., 2019), the U.S. EPA, and the California EPA. Recently the key characteristics of male and female reproductive toxicants (Arzuaga et al., 2019; Luderer et al. 2019) and of endocrine disrupting chemicals (La Merrill et al., 2020) have been described and those for other toxicant areas are in development. For more information https://keycharacteristics.org.

Bio

Martyn Smith is Professor of Toxicology and the Kaiser Endowed Chair of Cancer Epidemiology in the Division of Environmental Health Sciences in the School of Public Health at the University of California Berkeley. He received his Ph.D. in Biochemistry from St. Bartholomew's Hospital in London and did Post-Doctoral training in toxicology at the Karolinska Institute in Stockholm. Dr. Smith is a laboratory scientist with expertise in molecular epidemiology, toxicology and genomics, and his research is aimed at finding the causes of chronic diseases, including cancer and diabetes. He currently teaches Toxicology and Health Risk Assessment and mentors graduate students and postdoctoral scholars in the Molecular Toxicology, Epidemiology and Environmental Health Science programs. Dr. Smith is a Fellow of the American Association for the Advancement of Science. He received the 2010 Children's Environmental Health Network Award, became an Elected Fellow of the

Collegium Ramazzini in 2012, and received the Alexander Hollaender Award from the Environmental Mutagenesis and Genomics Society in 2014. Since its inception in 1987, Smith has directed the Superfund Research Program (SRP) Center at the University of California, Berkeley (UC Berkeley). This program combines basic research, engineering, population studies, training, and community engagement to understand cumulative impacts from multiple environmental stressors. Smith is best known for his work on benzene toxicity, the exposome concept and the key characteristics framework, which helps risk assessors better identify, organize, and summarize the potential health risks of different chemicals. His most recent work uses machine learning, AI and molecular modeling to predict toxicity.

Susan Norris

Advancing evidence decision frameworks to address social equity, environmental justice, and stakeholder engagement

Abstract

Data and evidence on benefits and harms form only one element of decision-making with respect to interventions intended to prevent and mitigate the adverse effects of substances in the environment. Other potential considerations include equity, cost, economic evaluations, availability of alternatives, feasibility of implementation, human rights, environmental justice, sociocultural acceptability, and the relative value placed on outcomes. Evidence-to-decision (EtD) frameworks help expert panels, policy-makers and other decision-makers use evidence in a structured and transparent way to inform recommendations, decisions, and policies. However, these frameworks have largely been developed to make recommendations in the field of clinical medicine. This presentation will summarize, compare, and contrast selected EtD frameworks in current use in clinical medicine, public health, and environmental health. There is a need to develop a framework for decision-making related to environmental health interventions which will explicitly include a broad set of considerations well beyond benefits and harms. Such a framework will lead to more transparent, fair, and inclusive processes for making valid and equitable decisions that reflect the voices of persons who are most impacted by toxic chemicals and pollution.

Bio

Dr. Norris has extensive experience with evidence appraisal and synthesis and guideline development related to clinical medicine and public health. She was Secretary of the WHO Guidelines Review Committee for 8 years, where she was responsible for quality assurance WHO's guidelines, training of WHO staff, quality improvement, and methods development related to public health guidelines. She was responsible for the *WHO handbook for guideline development* (2nd edition, 2014) and led numerous initiatives within WHO to improve guideline quality and production, including the development of a toolkit for rapid advice guidelines in public health emergencies.

Dr. Norris received her MD and MSc in Experimental Surgery from the University of Alberta, Canada, and MPH from the University of Washington, USA. She was board certified in both general surgery and family medicine and practiced primary care for 10 years, including in low-resourced settings. Dr Norris was involved in the development of evidence-based health system and care processes at a large health delivery organization and worked at the US CDC where she supported the development of guidelines on diabetes mellitus. Dr Norris was an Associate professor in clinical epidemiology at the Oregon Health & Science University (USA), where she led guideline projects for the US Preventive Services Task Force and the National Institutes of Health. She was principal investigator for a number of US federal grants, including projects focusing on conflict of interest in guidelines, selective outcome reporting, and sources of bias in non-randomized studies. She is currently an independent consultant.

Table of Contents (Presentations)

Applying systematic review methodology for the assessment of endocrine disruptors: the SYRINA approach

Anna Beronius, PhD, ERT (anna.beronius@ki.se)
Institute of Environmental Medicine, Karolinska Institutet

1

Endocrine disruptors (EDs)

"exogenous substances or mixtures that alter function(s) of the endocrine system and consequently cause adverse effects in an intact organism, or its progeny, or (sub)populations"

- WHO/IPCS 2002

2

1

Endocrine disruptors (EDs)

- Serious health effects, early development specifically vulnerable

- Complex toxicity and risk assessment

- Uncertainties

- Controversies
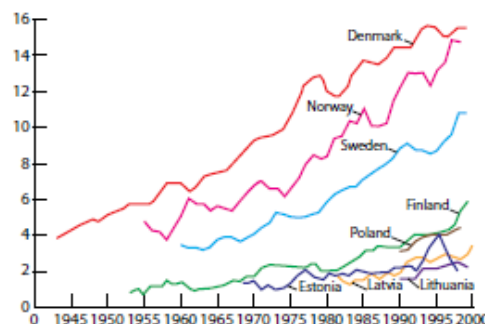
Figure 2.2. Trends in incidence of testicular cancer in northern Europe. Age-standardized (World standard population) by year of diagnosis and country. From Richiardi et al. (2004; Used with publisher's permission).

Beronius   Figure source: State-of-the-science of Endocrine Disrupting Chemicals. WHO-UNEP 2013.   2021-02-10   3

3

Development of a framework for systematic review and integrated assessment of EDs

- The goal: to propose an approach that
  - → increases structure and transparency
  - → promotes inclusion of all relevant data
  - → facilitates conclusions based on integration of several streams of evidence
  - → builds on existing systematic review methodology and approaches (e.g. IARC, NTP/OHAT approach, Navigation Guide, EFSA guidance)

- Two international workshops (2014 and 2015) with experts from Europe, the US, Canada and Australia

The proposed SYRINA framework
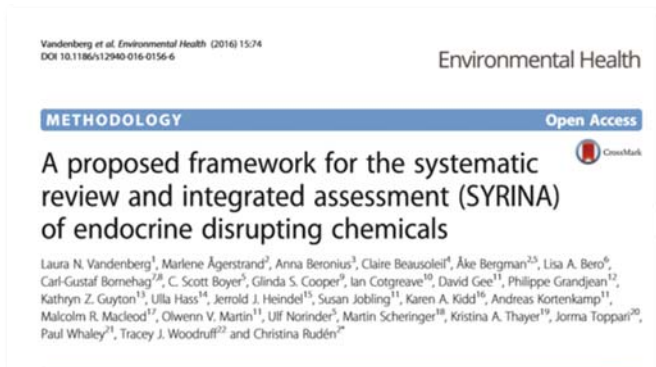
Vandenberg et al. 2016. Environmental Health 15:74
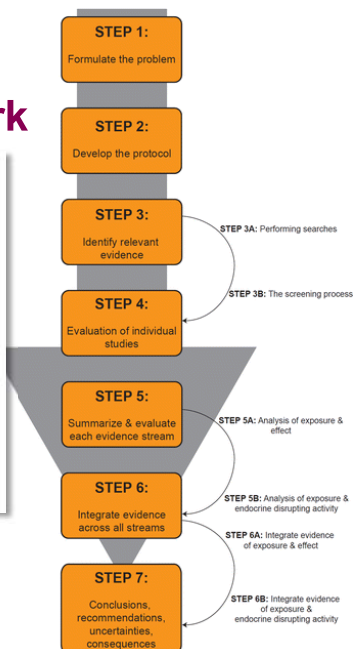
5

The proposed SYRINA framework

Streams of evidence
- Human data
- Ecotoxicological/wildlife data
- Toxicological *in vivo* data
- Toxicological *in vitro* data
- *In silico* data
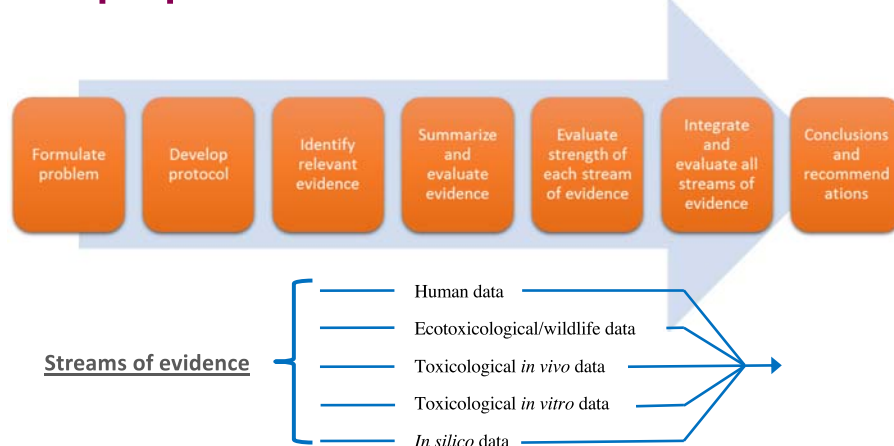
Based on the WHO definition

6

SYRINA steps

- **Step 1:** Formulate the problem
- **Step 2:** Develop the protocol
- **Step 3:** Identify relevant evidence
- **Step 4:** Summarize and evaluate evidence
- **Step 5:** Evaluation of each stream of evidence
- **Step 6:** Integrating evidence streams
- **Step 7:** Conclusions and recommendations

7

Step 6: Integrating evidence

a) for adverse effect:

b) for endocrine activity:

8

Step 7: Conclusions and recommendations

Strength of Evidence: Endocrine Disrupting Activity					
Strong	Probable EDC	Probable EDC	Known EDC	Known EDC
Moderate	Possible EDC	Possible EDC	Probable EDC	Known EDC
Weak	Not classifiable	Not classifiable	Possible EDC	Probable EDC
No data	Not classifiable	Not classifiable	Possible EDC	Probable EDC
	No data	**Weak**	**Moderate**	**Strong**

Strength of Evidence: Association Between Exposure and Health Outcome

SYRINA allows identifying substances as
- possible EDC,
- probable EDC, or
- known EDC

EU scientific criteria and process for identifying EDs implemented 2018

- For plant protection products and biocides

- Based on the WHO definition

- Calls for application of systematic review methodology to select relevant data other than regulatory studies

- Substances identified as ED or not ED
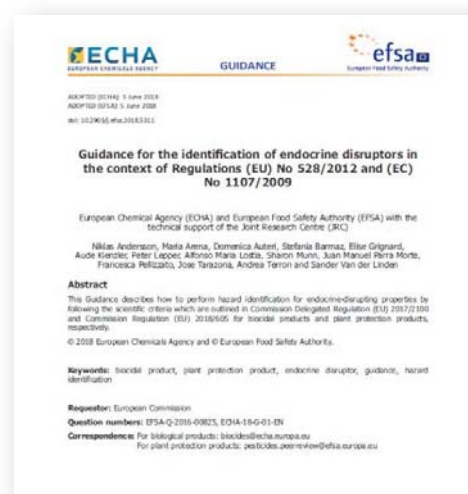
On-going SYRINA case study

- Evaluating evidence for Triphenyl phosphate (TPP)

- Lessons learned (so far)
  - → requires a lot of time and expertise
  - → refinements/clarifications to the SYRINA approach, e.g.
    - Prioritization of effects
    - Grouping of evidence into lines of evidence
    - Separating the assessment of mammal and non-mammal adversity

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Continued development of systematic methods for assessment of chemicals

- Systematic evidence mapping

- Recommendations for the conduct of systematic reviews in toxicology and environmental health research (COSTER)

- Applying the EU process for ED assessment to non-pesticides

- Facilitating systematic searches for ED evidence

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Acknowledgements, authors of the SYRINA framework

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Olwenn Martin, Brunel University

Ulf Norinder, Swetox

Martin Scheringer, Leuphana University

Kristina Thayer, NIEHS, OHAT/NTP

Jorma Toppari, University of Turku

Paul Whaley, Lancaster University

Tracey Woodruff, University of California

Jerrold Heindel, NIEHS

Thank you for your attention

Two POPs: Dioxins and PFAS
Different Levels of Evidence,
Different Times

Linda S. Birnbaum, Ph.D., D.A.B.T., A.T.S.
Scientist Emeritus and Former Director, NIEHS and NTP
Scholar in Residence, Duke University

Conducting Evaluations of Evidence that are Transparent, Timely and Lead to Health-Protective Actions. Feb 8-11, 2021

Why the Interest in Dioxins???

- 1899 – Chloracne Characterized
- 1929 – PCBs produced commercially
- 1947 – "X" Disease in cattle
- 1949 – Nitro, West Virginia
- 1957 – Chick Edema Disease; TCDD identified in TCPs
- 1962-1970 – Agent Orange use in Southeast Asia
- 1968 – "Yusho" oil disease
- 1971 – Times Beach; TCDD causes birth defects in mice

- 1973 – PBB contamination in Michigan
- 1976 – Seveso, Italy
- 1978 – Kociba rat cancer study
- 1979 – "Yucheng" oil dieases
- 1981 – Capacitor fire in Binghamton, NY
- 1985 – 1st US EPA health assessment of TCDD
- 1991 – NIOSH cancer mortality study of US workers
- 1999 – Belgium dioxin poisoning; Viennese poisoning

PFAS-exposure related health concerns began 1960s

2006: EPA invites 8 major companies to phase out PFOA by 2015 (95% reduction by 2010)

1947: PFAS production begins at 3M plant in MN

1978: Unpublished study shows adverse effects of PFOA in monkeys

1981: Concerns about birth defects in children born to women workers

2009: Chemours commercially manufactures GenX as PFOA substitute

1980: PFAS detected in serum of workers

2000: PFOA and PFOS detected in 100% of Americans in study; 3M announces phase-out of PFOA

1987: PFOA causes cancer in rat study

PTFE (Teflon) invented

PFOS-based stain & water resistant products

PFOS-based fire fighting foam

2000-2002: DuPont begins producing PFOA at Chemours facility in Fayetteville, NC

| 1930s | 1940s | 1950s | 1960s | 1970s | 1980s | 1990s | 2000s | 2010s | Present |

PFOS & PFOA begin to be produced PTFE-based non-stick coatings produced

PFOA-based protective coatings

PTFE-based waterproof fabrics PFNA & fluorotelomers begin to be produced

2001: DuPont sued in class action lawsuit

1998: Samples from U.S. blood donors shown to contain PFAS

2004: DuPont settles class action suit (>80,000 plaintiffs) for $343 million; settlement funds C8 Health Study

1962: DuPont raises concerns re: health risks of PFAS in internal document

1993: 3M begins to monitor PFOA in workers

2012: Immune system effects related to PFAS reported in children

2015: Researchers publish report of novel PFAS (including GenX) in Cape Fear River

3M ‹DUPONT› Chemours SOLVAY

3

Structures

Dioxins

2,3,7,8-Tetrachlorodibenzo-*p*-dioxin

"The Most Toxic Man-Made Compound"

PFAS

PFOA

PFOS

PFHxA

PFHxS

4

How Many?

Dioxins

- 2,3,7,8-TCDD: Prototype
- PCDD/Fs
- PCBs, Napthalanes, Azo/Azoxybenzens (Major industrial Compounds)
- Although 209 PCDD/Fs and 208 PCBs, only ~29 are TCDD-like
- Some PBDD/F/Bs and PXDD/F/Bs

PFAS

- Total number of PFA - >9,000 chemicals
  - Includes products, impurities and degradants
    - Teflon
    - Scotchguard
    - Aqueous Film Forming Foams (AFFFs)
  - Many unknown formulation
- Resistant to grease, water & oil
  - Surfactants, stain repellants
  - Fire suppression - AFFF
- Persistent, mobile and bioaccumulative
- Emergence of short-chain alternatives - less well studied
  - Few studied – same effects as long chains

5

Major Sources

Dioxins

- Incineration (municipal, medical waste, hazardous waste)
- Other Combustion Processes (backyard burning, volcanoes and forestfires)
- Chlorine Bleaching of paper and Pulp Products
- Metal Smelting, Refining and Processing
- Past Sources – Chlorinated herbicide and biocide production; Leaded Gasoline

PFAS

- Diverse group of chemical compounds used in industry and consumer products worldwide since 1950s
- Contaminant in Drinking water
- Found in various products:
  - Carpet and fabric
  - Food paper
  - Pots and Pans
  - Clothing
  - Cardboard packaging
  - Firefighting foams (AFFF)
- Food – Fish, Seafood, Meat, Dairy, Plants

6

Dioxins Exposure

SOURCES

TRANSPORT

DEPOSITION

FOOD SUPPLY

Reentrainment

Industrial Processes

Combustion

Runoff Erosion

Direct Discharge

7

PFAS Exposure

Consumer Products

Human Exposure

Industry

Waste Infrastructure

AFFF

Transfer to Infants
- Breast milk
- Cord blood

Environment
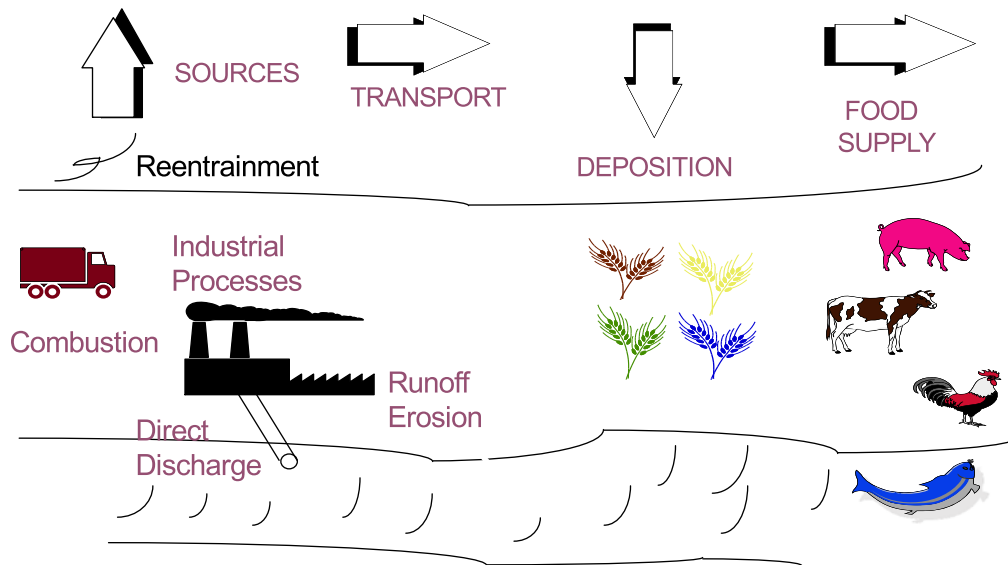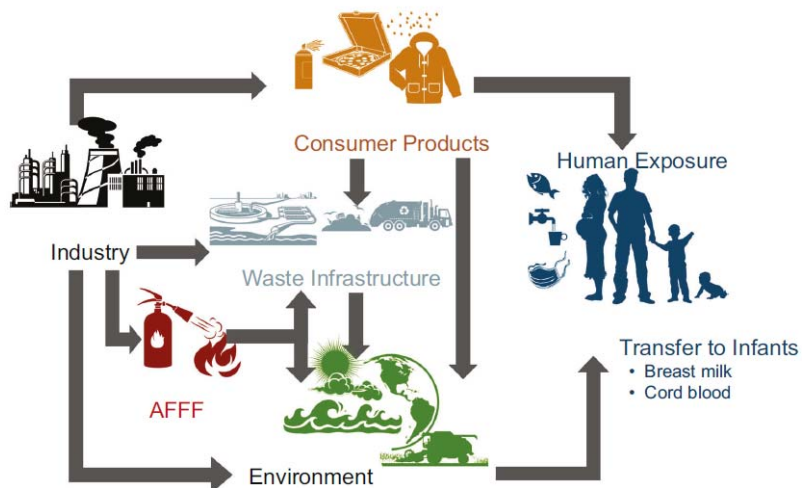
Sunderland et al., J Expos Sci & Epidemiol, 2019

8

4

Who's Exposed?

Dioxins
- General Population
- Occupational and Accidental Exposures
- Decline since peak ~1980s
- ~1% of general population have levels 3X average
- Higher Exposure to Nursing Infants, Subsistence Hunters/Fishers

PFAS
- General Population
- Occupational and Accidental Exposures
- Detected in humans globally
- >98% of people in the U.S. have measurable amounts of PFAS
- Levels of PFOA and PFOS have declined following phase-outs
- Changes in exposure to other PFAS are less pronounced
  - both increasing and decreasing

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Dioxin Mechanism of Action
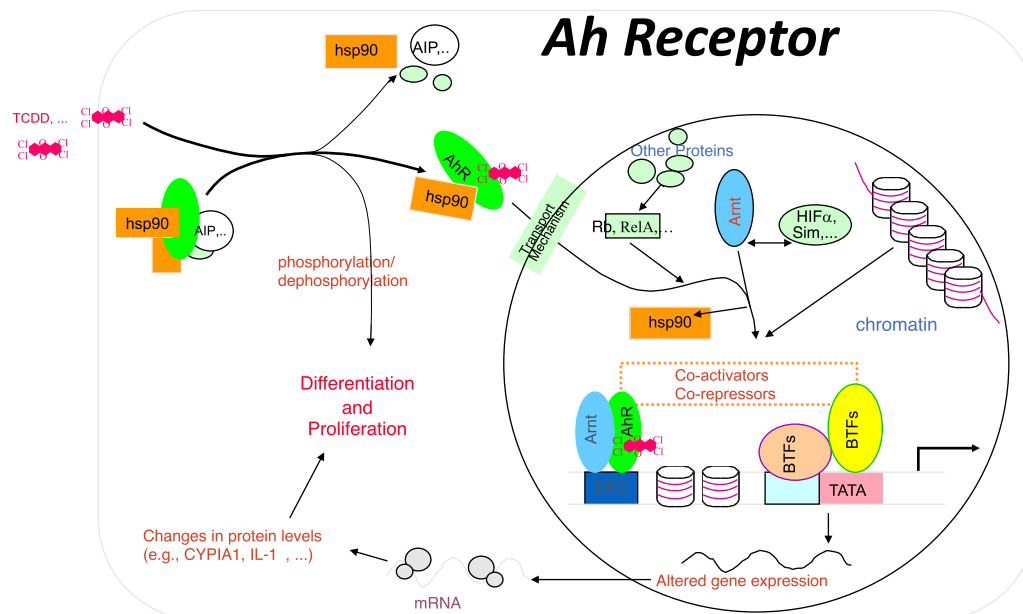
Ah Receptor

10

Multiple Mechanisms of PFAS toxicity

- Activation of PPARs
- Alternate receptor: AhR, CAR, PXR, FXR +++
- Inhibiting fatty acid transport
- Interfering with mitochondrial function
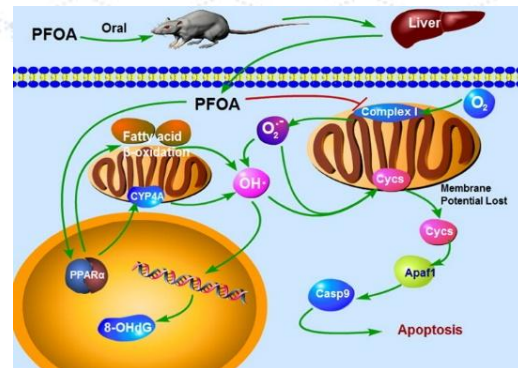
Li et al., 2017

Rebecca Fry, UNC

Laundry List of Effects

Dioxins
- Multiple effects in multiple tissues of both sexes of multiple species throughout the Vertebrate Kingdom
- Cancer and Non-Cancer
- Developmental and Immune
- Effects Observed at High End of General Population

PFAS
- Multiple effects in multiple tissue of both sexes of multiple species throughout the Vertebrate Kingdom +++
- Cancer and Non-cancer
- Developmental and Immune
- Effects Observed at High End of General Population

Hazard Assessments (CA+NonCA)

Dioxins

- Cancer – 2,3,7,8-TCDD
  - US EPA, 1985 – Probable
  - IARC, 1997 –Known
  - NTP, 2001 – Known
- Non-Cancer (TEQ)
  - US EPA, 2010

  IARC – PCB126 - Known

  NTP – PCBs and PBB – Reasonably Anticipated to be Carcinogenic

PFAS

- Cancer – PFOA
  - IARC - Possible
- Non-Cancer
  - US EPA
    - Lifetime Health Advisory – PFOA, PFOS
    - PFBS, GenX
  - FDA

US Regulations

Dioxins

- Comprehensive Environmental Response, Compensation and Liability Act (CERCLA) / Resource Conservation and Recovery Act (RCRA)
- Hazardous Air Pollutants for Hazardous Waste Combustors and Clean Air Act
- Toxic Substances Control Act (TSCA)
- Emergency Planning and Community Right-to-Know Act (EPCRA)
- Safe Drinking Water Act (SDWA)

PFAS

- EPA
  - Lifetime Health Advisories for Drinking Water – 70 ppt PFOA+PFOS
    - NO regulation of ground water
    - NO determination of 'Hazardous Substance'
  - 172 PFAS added to TRI (in NDAA 2020 Appropriation)
- FDA
  - Food Contamination
- Department of Defense
  - No PFAS in AFFF in practice/training
  - No PFAS in Food Packaging
- FAA
  - No PFAS required in AFFF in domestic airports

States, and Congress, moving ahead!

Obfuscation and Delay (same tactics, same players)

Dioxins
- Unwanted Contaminants
- Chloralkali Production, Biocides, Combustion
- Volcanos and Forest Fires
- Agent Orange, Times Beach, Nitro West Virginia
- Cast Doubt
- Dow Chemical (Monsanto)
- Industrial Production Controlled-→Decreasing in Environment and People

PFAS
- Highly Valuable Industrial Products
- Large volume, Big profits
- Unfortunate Substitution
  - Short Chains can have same effects as long chains
- Ignore Life cycle
- Polymers – have monomers in production, during use, and disposal
- Class Approach + Essentiality
- 3M, DuPont, Chemours, Solvay
- DuPont+Dow-→Corteva

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PFAS = The Dioxins of the 21st Century

BUT, MUCH WORSE!!!

Thank you!!!

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17

Animal *and Human* Studies Show Wide Range of Health Effects

PFOA and/or PFOS

- Testicular cancer
- Kidney cancer
- Ulcerative colitis
- High cholesterol
- Pregnancy-induced hypertension
- Thyroid disruption
- Hormonal changes
- Liver malfunction
- Obesity

- Immunotoxicity, eg interference with child vaccine response
- Lower birth weight and size
- Delayed puberty, decreased fertility, early menopause
- Reduced testosterone
- Prostate cancer
- Ovarian cancer
- Bone density decrease

9

18
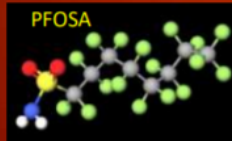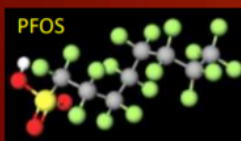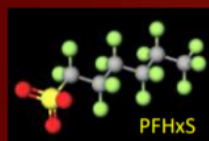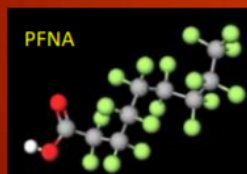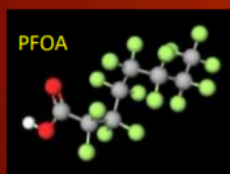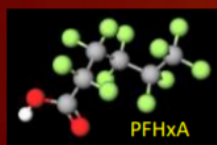
COMEAP
COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Divergent views on quantification of all-cause mortality based on associations with long-term average concentrations of NO$_2$

Alison Gowers, Public Health England
Roy Harrison, University of Birmingham

Divergent Science Perspectives Workshop   8 – 11 February 2021

1

Overview

- Background and introduction
- Majority view
- Dissenting view

2

COMEAP

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

COMEAP report on mortality associated with long-term average concentrations of NO_2

BACKGROUND AND INTRODUCTION

COMEAP

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

Associations of long-term average concentrations of nitrogen dioxide with mortality

A report by the Committee on the Medical Effects of Air Pollutants

Chairman: Professor Frank Kelly

Chairman of the QUARK Working Group on Nitrogen Dioxide: Professor Roy Harrison

Request from Defra:
- How to quantify the benefits of reducing long-term average concentrations of NO_2.
- To support the development of Air Quality Plans to reduce NO_2 concentrations

COMEAP 2018
www.comeap.org.uk

Mortality estimates for NO$_2$ - HRAPIE

Pollutant metric	Health outcome	Group	RR (95% CI) per 10 µg/m³	Range of concentration
NO$_2$, annual mean	Mortality, all (natural) causes, age 30+ years	B*	1.055 (1.031−1.080)	>20 µg/m³

Source of background health data	Source of CRF	Comments
MDB (WHO, 2013c), rates for deaths from all natural causes (ICD-10 chapters I–XVIII, codes A–R) in each of the 53 WHO Regional Office for Europe countries, latest available data	Meta-analysis of all (11) cohort studies published before January 2013 by Hoek et al. (2013); RR based on single-pollutant models	Some of the long-term NO$_2$ effects may overlap with effects from long-term PM$_{2.5}$ (up to 33%); this is therefore recommended for quantification under Group B to avoid double counting in Group A analysis

New meta-analysis

Random effects summary HR: 1.023 (95% CI 1.008, 1.037) per 10 µg/m³ NO$_2$
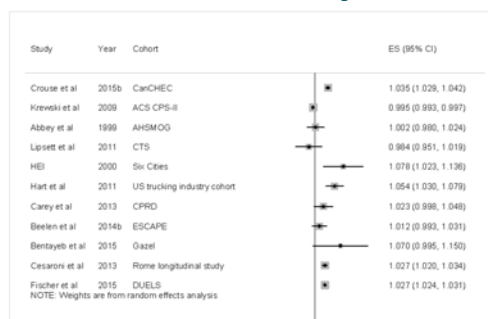
HRs (95% CI) per 10 µg/m³ for cohort studies reporting associations between NO₂ and all-cause mortality

To note:
- **All-cause** mortality only considered (not cause-specific mortality)
- Cut-off date for literature review – **October 2015** (new studies and meta-analysis now available)
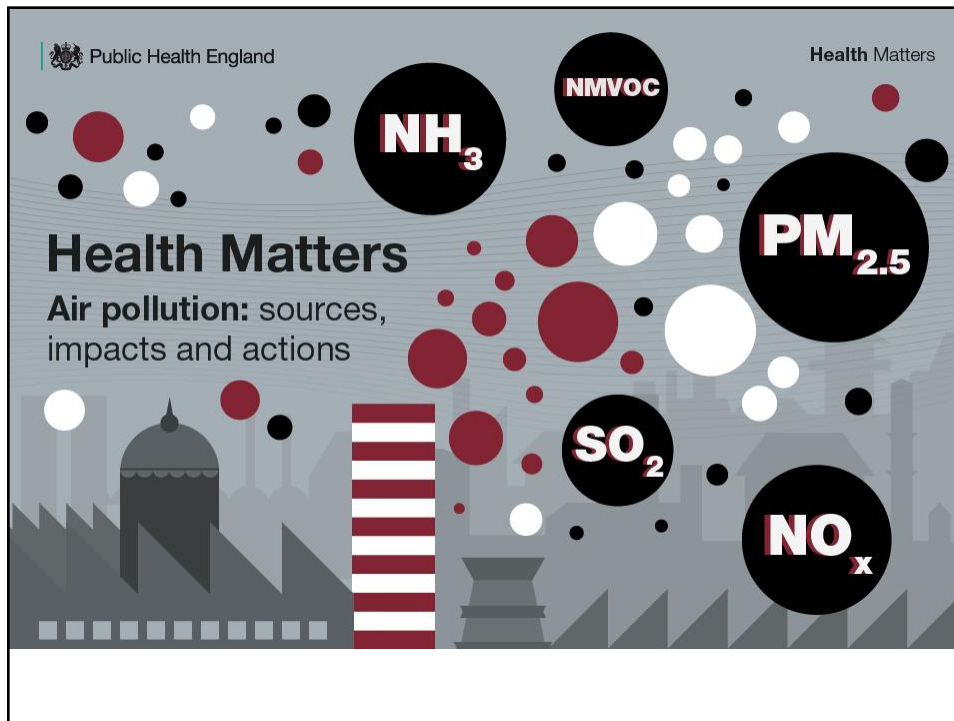
7
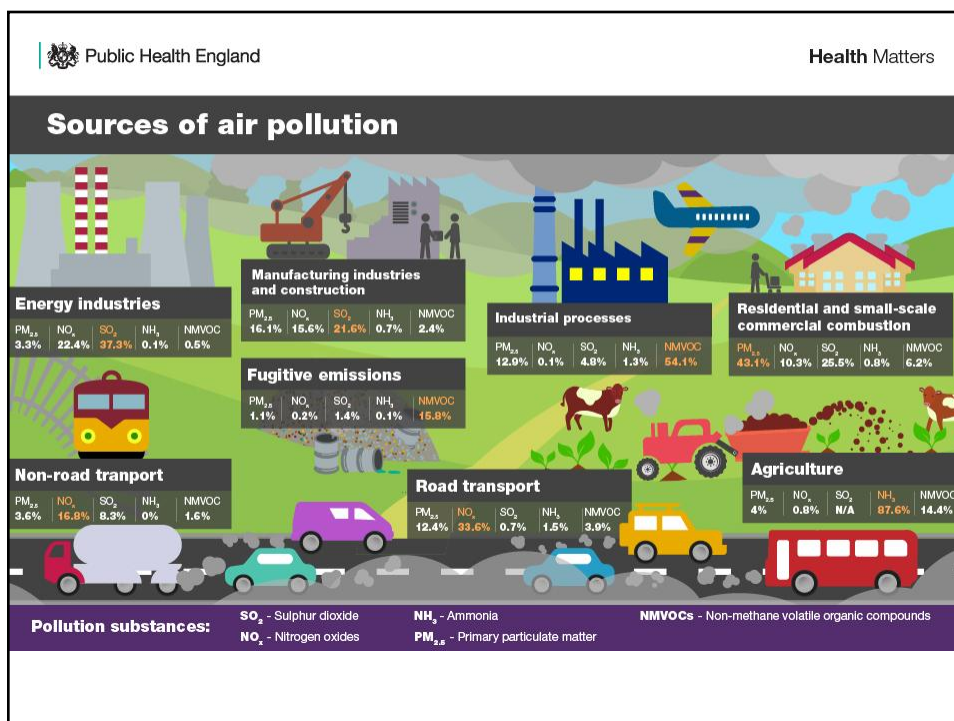
8

Unadjusted coefficient for NO_2

Reflects:

- any causal effect of NO_2
- and also, to some extent, the effects of other pollutants correlated with NO_2

Correlated pollutants:

- $PM_{2.5}$
- other components of the air pollution mixture eg
  - Ultrafine particles
  - Black Carbon
  - Volatile Organic Compounds etc

9

COMEAP

COMMITTEE ON THE MEDICAL EFFECTS OF AIR POLLUTANTS

COMEAP report on mortality associated with long-term average concentrations of NO_2

MAJORITY VIEW

10

One and two pollutant models

- Air pollution epidemiology uses models which regress a health outcome against estimated pollutant exposures in either a longitudinal or cross-sectional design
- Evaluation of chronic effects of exposure upon mortality uses cross-sectional designs, corrected for confounders such as smoking and deprivation
- Single pollutant models attribute all of the variance in the health outcome to a single pollutant (after correction for confounders)
- Two pollutant models should allow the effects to be quantitatively attributed to each of the two pollutants if both account for some of the effects

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Independence from PM mass

Using HRs (per IQR) from studies reporting results from single and two/multi-pollutant models for NO_2 and PM:

Compared:
- HRs from single-pollutant models with
- Combined adj HRs (NO_2 adj for PM; PM adj for NO_2)

➢ The combined effect using coefficients each adjusted for the effects of the other, is either similar to or only little higher than what would be estimated for either $PM_{2.5}$ or NO_2 alone

12

Hazard ratios (HRs) expressed per interquartile range (IQR) from single and two pollutant models for NO$_2$ and PM$_{2.5}$

Study (additional sig figs for HRs obtained from the authors)	Corr NO$_2$/ PM$_{2.5}$	NO$_2$ IQR (µg/m3)	PM$_{2.5}$ IQR (µg/m³)	NO$_2$ adj PM$_{2.5}$	PM$_{2.5}$ adj NO$_2$	Combined NO$_2$ adj / PM adj	PM$_{2.5}$ Single	NO$_2$ Single
Cesaroni et al 2013	0.79	10.7	5.7	1.026	1.004	**1.030**	1.023	**1.029**
Carey et al 2013 pers comm	0.85	10.7	1.9	1.001	1.023	**1.024**	**1.023**	1.022
Beelen et al 2014 14 cohorts	0.2- <0.7	10.0	5.0	1.007	1.060	**1.067**	**1.070**	1.015
Fischer et al 2015 PM$_{10}$	0.58 (with PM$_{10}$)	10.0	2.4	1.019	1.010	**1.029**	1.019	**1.027**
HEI 2000 41 cities	-0.08	81.4 (min,max)	24.5 (min,max)	0.90	1.22	**1.09**	1.15	0.95
Jerrett et al 2013	0.55	7.7	5.3	1.025	1.015	**1.040**	1.032	1.031

13

Coefficient for NO$_2$ adjusted for PM$_{2.5}$

Excludes, as far as possible:
- effects associated with PM$_{2.5}$ concentrations, and other components of the air pollution mixture that are more closely correlated with PM$_{2.5}$ concentrations than with NO$_2$ concentrations

Reflects:
- any causal effect of NO$_2$ and also, to some extent, of other pollutants closely correlated with NO$_2$

➢ The extent to which the effect is likely to be causally related to NO$_2$ is unclear

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7

Two-pollutant models: challenges

- No tests for interaction

- Overlapping confidence intervals

- Possible transfer of effect in the presence of exposure misclassification

- High correlation between pollutants

➢ Use studies with lower correlation to make an informal estimate of a representative reduction of NO_2 coefficient on adjustment for PM

15

Adjusting pooled single pollutant coefficient with paired % reductions within each of 4 studies (HR per 10 µg/m^3)

Indicator pollutant	Unadjusted coefficient	Options for mutually adjusted coefficients			
		Jerrett et al 2013	Fischer et al 2015 (PM$_{10)}$	Beelen et al 2014	Crouse et al 2015 (with O$_3$)
NO_2 % reduction adj for PM	n/a	19%	29%	53%	13%
SP model alone or with % reduction	1.023 (1.008, 1.037)	1.019	1.016	1.011	1.020
PM$_{2.5}$ % reduction adj for NO_2	n/a	53%	46%	14%	68%
SP model alone or with % reduction	1.06 (1.04, 1.08)	1.029	1.033	1.053	1.019

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8

Reduction of the unadjusted coefficient for NO_2

- On the basis of the two pollutant model results, using studies with lower correlations between $PM_{2.5}$ and NO_2, reduce the coefficient by 20% to allow for effects due to $PM_{2.5}$

- To allow for the possible effects of other closely correlated pollutants, reduce the coefficient further by 30-70%

- Gives an overall reduction to 25-55% of the unadjusted coefficient to capture the effects of NO_2 alone

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Health burden and health impact

- Exposure-response coefficients from the epidemiological models can be used to estimate either a health burden or a health impact

- Health burden describes the effect of a given level of pollutant or combination of pollutants upon a health outcome in an exposed population (eg an annual mortality burden of current pollution levels)

- Health impact describes the health benefits to an exposed population that would be expected if levels of air pollution were reduced (eg the mortality benefits of a reduction of $1 \ \mu g \ m^{-3}$)

18

COMEAP – HIA Recommendations

HIA of reductions in all traffic-related pollutants:

- Use summary unadjusted NO_2 coefficient:

➢ 1.023 (95% CI 1.008, 1.037) per 10 μg/m^3

HIA of interventions which target NO_x emissions

- Use 25 – 55% of summary unadjusted coefficient

➢ 1.006 – 1.013 per 10 μg/m^3 – "central range"

    Informal expert judgement approach equivalent to:

        o   Reduction of approx 20% on adjustment for PM

        o   30 - 70% of adjusted coefficient may be causal

Illustrative range of burden estimates for long-term exposure to air pollution UK 2013

An effect equivalent to:

28,000 - 36,000 deaths at typical ages, and an associated loss of 328,000 – 416,000 life years, (effects **down to zero** concentration included).

Compares with 29,000 deaths/330,000 life year lost for PM$_{2.5}$ single pollutant coefficient; 22,000 deaths/252,000 life years lost for NO$_2$ single pollutant

16,000 – 19,000 deaths at typical ages and an associated loss of 181,000 – 224,000 life years, (effects down to a **cut-off of 5 μg/m^3 NO$_2$/ 7 μg/m^3 PM$_{2.5}$**)

Compares with 13,000 deaths/151,000 life year lost for PM$_{2.5}$ single pollutant coefficient; 16,000 deaths/181,000 life years lost for NO$_2$ single pollutant

Results have uncertainty associated with them, but not able to quantify that uncertainty.
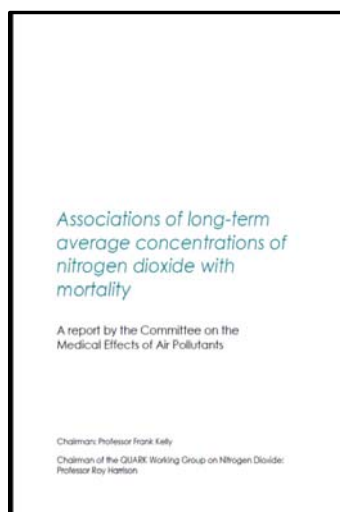
COMEAP report on mortality associated with long-term average concentrations of NO$_2$

DISSENTING VIEW

Chapter 10:
Views of the dissenting group

- Background

- Evidence for causality

- Uncertainty in HRs in two-pollutant models

- Purpose of impact and burden calculations

- Summary

- Annexes A and B

Chapter 12 (12.3.1): **Statement** of disagreement with the conclusion of the majority

Associations of long-term average concentrations of nitrogen dioxide with mortality

A report by the Committee on the Medical Effects of Air Pollutants

Chairman: Professor Frank Kelly

Chairman of the QUARK Working Group on Nitrogen Dioxide: Professor Roy Harrison

22   Quantification of all-cause mortality based on associations with long-term average concentrations of NO$_2$

Statement of disagreement

- Causality

- The decision to estimate the burden of mortality and to extrapolate to zero concentration of NO_2

- The use and interpretation of two-pollutant models

- The inadequate consideration of uncertainties, including heterogeneity within the evidence

Causality – possible chance or bias?

- The weight of evidence supporting a possible causal relationship from adverse health effects is from studies of **short-term** exposure

- Chance? New meta-analysis:
  - Lower HR than estimate used by WHO HRAPIE
  - Lower 95% CI nearer the null than estimate used by WHO HRAPIE
  - Trim and fill – indicated possible small study bias

- Confounding and bias
  - Larger effect in administrative cohorts – possible residual confounding
  - Correlation with other pollutants
    - Difficulties in interpreting multi-pollutant model results
    - Differences in correlations/ratios have implications for transferability

Causality – Bradford Hill considerations

- **Strength of association:** Not strong or statistically secure

- **Consistency:** Limited (high heterogeneity)

- **Specificity:** Neutral/weak (associations with other pollutants similar)

- **Temporality:** Not relevant

- **Biological gradient:** Positive linear associations are consistent with causality of NO_2 or a closely correlated pollutant

- **Plausibility:** Substantial evidence for effects of short-term exposure on the respiratory system. Less evidence for effects of long-term exposure. Ratio of cohort to time-series HRs for NO_2 approx. 3:1; suggests short-term effects may make substantial contribution to associations in cohort studies

- **Analogy:** Reasonable (effects of other ambient pollutants)

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Multi-pollutant models

- It is not known whether there is a statistical **interaction** (ie whether the association with NO_2 varies with the concentration of $PM_{2.5}$)

- **Correlation** of pollutant concentrations can lead to model instability

- **Exposure measurement error** (especially if differential) can result in
  - bias in effect estimates
  - loss of precision
  - effect transfer

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Impact and burden calculations using NO_2

Burden estimates: to communicate the scale of effect on public health
- Lack of public understanding of meaning of "attributable deaths"
- Need (QUARK) to undertake further work on multi-pollutant issues
- Evidence base too limited, uncertain and complex
- Disagree with extrapolation beyond range of studied concentrations

Impact assessments: to support policy analysis
- Use of single-pollutant coefficient for interventions targeting emissions of multiple pollutants, if used to support comparisons of possible policies

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Level of certainty required: dissenting view

In our view there is an important difference between the level of conviction needed to accept that an association reported by epidemiological studies is likely to represent a causal association and that needed to allow a reliable estimate of the quantitative effects of exposure to be made.

Associations of long-term average concentrations of nitrogen dioxide with mortality

A report by the Committee on the Medical Effects of Air Pollutants

COMEAP 2018
www.comeap.org.uk

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14

The Key Characteristics of Carcinogens

Kate Z. Guyton, PhD DABT
Senior Toxicologist, *Monographs* Programme
International Agency for Research on Cancer, Lyon, France

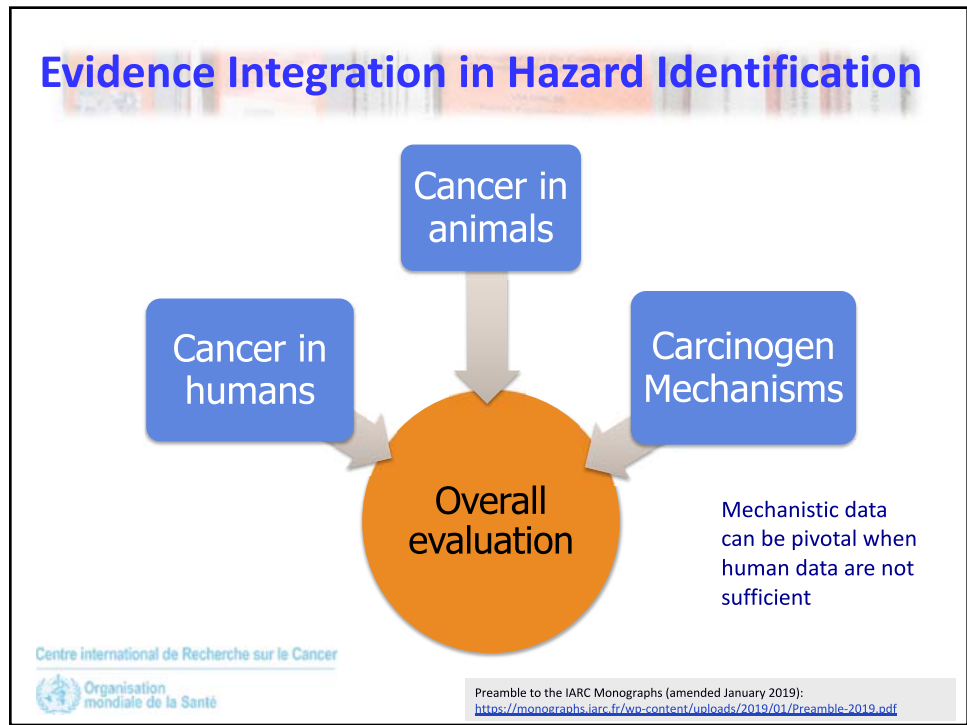International Agency for Research on Cancer

World Health
Organization

1

Conflict of Interest Statement

I declare no financial interests related to the subject matter of my presentation.

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2

Evidence Integration in Hazard Identification

Cancer in animals

Cancer in humans

Carcinogen Mechanisms

Overall evaluation

Mechanistic data can be pivotal when human data are not sufficient

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Preamble to the IARC Monographs (amended January 2019): https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

3

IARC Group 1 Classifications
Based on *Different* Mechanisms

Agent	Mechanistic Rationale	Year (Vol)
Ethylene oxide	Genotoxic, cytogenetic effects in human lymphocytes	1994 (Vol 60)
NNN and NNK	Uptake, metabolism, DNA/haemoglobin adducts in smokeless tobacco users	2004 (Vol 89)
Benzo[a]pyrene	Specific diolepoxide-induced DNA adducts, KRAS mutations in exposed humans	2005 (Vol 92)

Agent	Mechanistic Rationale	Year
2,3,7,8-TCDD	Ah receptor binding, subsequent effects	1997 (Vol 69)
2,3,4,7,8-Penta-chlorodibenzofuran	Same Ah receptor pathway as 2,3,7,8-TCDD	2009 (Vol 100F)

World Health Organization

4

2

Multiple Mechanisms of Group 1 Carcinogens

	Carcinogen			
Mechanisms	**Aflatoxin B1**	**Arsenic**	**Asbestos**	**Benzene**
DNA damage	+	+	-	+
Gene mutation	+	-	+	-
Chrom mutation	+	+	+	+
Aneuploidy	-	+	+	+
Epigenetic	+	+		+
Receptor signaling	-	+	+	
Other signaling	-	+		+
Immune effects	+	+	+	+
Inflammation	+	+	+	+
Cytotoxicity	+	+	+	+
Mitogenic	-	+		-
Gap junction	+	+		+

International Agency for Research on Cancer

World Health Organization

Guyton KZ, Kyle AD, Aubrecht J, Cogliano VJ, Eastmond DA, Jackson M, Keshava N, Sandy MS, Sonawane B, Zhang L, Waters MD and Smith MT. Mutat Res. 681(2-3):230-40, 2009.

5

Mechanistic Data: *Challenges*

IARC Monographs
Volume 100

Centre international de Recherche sur le Cancer

Organisation mondiale de la Santé

- How to search systematically for relevant mechanisms?
- How to bring uniformity across assessments?
- How to analyze the voluminous mechanistic database efficiently?
- How to avoid bias towards favored mechanisms?

6

10 Key Characteristics of Human Carcinogens

Key characteristics:
1. Is electrophilic or can be metabolically activated
2. Is genotoxic
3. Alters DNA repair or causes genomic instability
4. Induces epigenetic alterations
5. Induces oxidative stress
6. Induces chronic inflammation
7. Is immunosuppressive
8. Modulates receptor-mediated effects
9. Causes immortalization
10. Alters cell proliferation, cell death, or nutrient supply

- Chemical and biological properties of established human carcinogens
- Data on key characteristics can provide evidence of carcinogenicity
- Used to assemble data relevant to mechanisms of carcinogens– without needing an *a priori* hypothesis of the mechanism

- Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K (2016). Env Health Persp., 124(6):713-21.
- Guyton KZ, Rusyn I, Chiu WA, Corpet DE, van den Berg, M, Ross, M, Christiani DC, Beland FA, Smith MT (2018). Carcinogenesis, 39(4):614.
- IARC Scientific Publication No. 165: Tumour Site Concordance and Mechanisms of Carcinogenesis (2019). https://publications.iarc.fr/578.
- Smith MT, Guyton KZ (2020). Identifying carcinogens from 10 key characteristics: a new approach based on mechanisms. In: Wild CP, Weiderpass E, Stewart BW, editors. World Cancer Report: Cancer Research for Cancer Prevention. http://publications.iarc.fr/586.
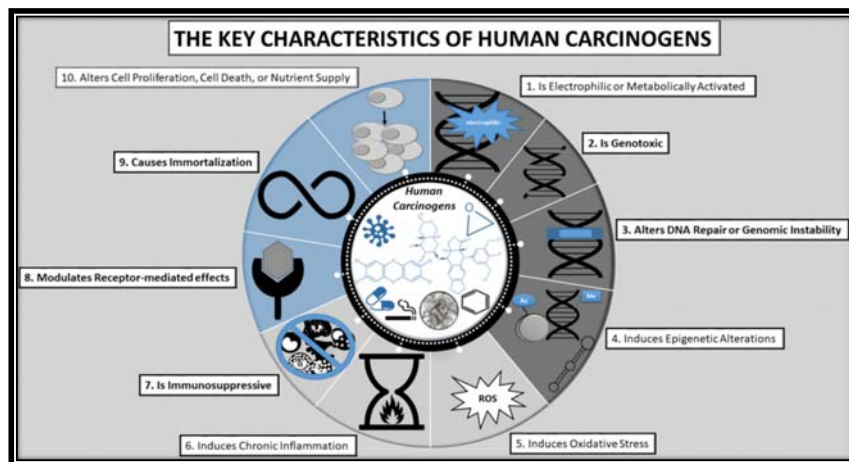
World Health Organization

- Guyton KZ, Rieswijk L, Wang A, Chiu WA, Smith MT (2018). Chemical Research in Toxicology, 31(12): 1290-1292.
- Smith MT, Guyton KZ, Kleinstreuer N, Borrel A, Cardenas A, Chiu WA, Felsher DW, Gibbons CF, Goodson WH, Houck KA, Kane A, La Merrill MA, Lebrec H, Lowe L, McHale CM, Minocherhomji S, Rieswijk L, Sandy MS, Sone H, Wang A, Zhang L, Zeise L, Fielden M (2020). Cancer Epidemiol Biomarkers Prev. 29(10):1887-1903.
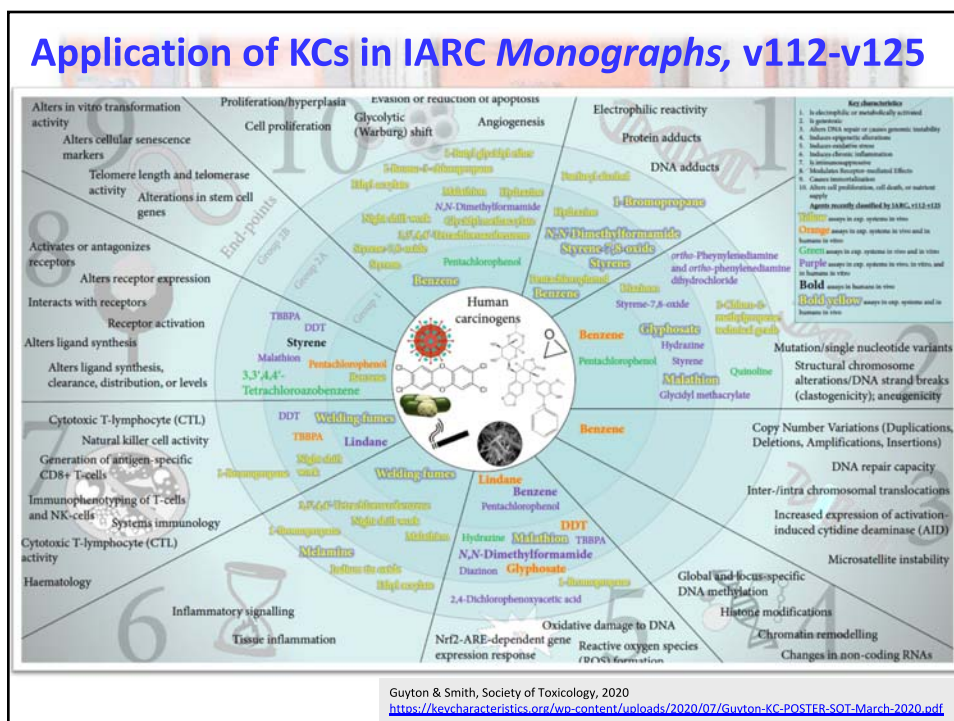- For more on the key characteristics of hazardous exposures, see: https://keycharacteristics.org/

World Health Organization

**Systematic Approach
Using Key Characteristics of Carcinogens**

Targeted searches for agent + each key characteristic

Organize results by key characteristics, species, etc

International Agency for Research on Cancer

World Health Organization

Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K (2016). *Env Health Persp.*, 124(6):713-21.

9

**Key Characteristics of Benzene:
An Adverse Outcome Pathway?**

Benzene Exposure

Electrophilic epoxides, aldehydes and quinones
Metabolic Activation

DNA Damage Mutations Chromosome aberrations
Genotoxicity

Stem Cell Transformation Proliferation Clonal Expansion
Altered Cell Proliferation

Leukemia

Source: MT Smith

10

5

An Adverse Outcome Network Involving 8 Key Characteristics — Benzene Exposure. Smith MT, Guyton KZ, Gibbons CF, Fritz JM, Portier CJ, Rusyn I, DeMarini DM, Caldwell JC, Kavlock RJ, Lambert PF, Hecht SS, Bucher JR, Stewart BW, Baan RA, Cogliano VJ, Straif K (2016). Env Health Persp., 124(6):713-21.

11

Application of KCs in IARC Monographs, v112-v125. Guyton & Smith, Society of Toxicology, 2020 https://keycharacteristics.org/wp-content/uploads/2020/07/Guyton-KC-POSTER-SOT-March-2020.pdf

12

Strong Evidence of KCs: Impact on Group 1, 2A and 2B Evaluations

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

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Preamble to the IARC Monographs (amended January 2019):
https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

13

Key Characteristics of Carcinogens: *Identifying Future Priorities*

14

Recent Classifications: 2019 Preamble

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited			
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Opium consumption

*Opium **is genotoxic** in experimental systems **(KC1)**

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Recent Classifications: 2019 Preamble

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Night shift work

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8

Recent Classifications: 2019 Preamble

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong*	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic cl...	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Night shift work

*Night shift work **induces chronic inflammation, is immunosuppressive**, and **alters cell proliferation (KCs 6, 7, 10)** in experimental systems

17

Recent Classifications: 2019 Preamble

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		
Limited		Strong	Probably carcinogenic (Group 2A)
	Sufficient	Strong (human cells or tissues)*	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

Acrolein

*Acrolein **is electrophilic; is genotoxic; alters DNA repair or causes genomic instability; induces oxidative stress and chronic inflammation; is immunosuppressive;** and **alters cell proliferation, cell death, or nutrient supply** (KCs 1, 2, 3, 5, 6, 7, 10)- primarily from studies in human primary cells and studies in experimental systems, supported by studies on DNA adducts in humans
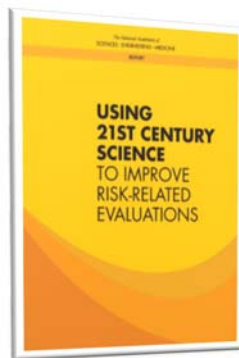
18

Recent Classifications: 2019 Preamble

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient		Strong (exposed humans)	Carcinogenic (Group 1)
	Sufficient		
		Strong	Probably carcinogenic (Group 2A)
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
	Sufficient		Possibly carcinogenic (Group 2B)
		Strong*	

Callout:

Sufficient bioassay + **strong** mechanistic evidence:
- 1-Butyl glycidyl ether
- 1-Bromo-3-chloropropane
- Cupferron

Strong mechanistic evidence alone:
- Crotonaldehyde
- Arecoline

*1-Butyl glycidyl ether & 1-bromo-3-chloropropane **alter cell proliferation, cell death or nutrient supply (KC10)** in experimental systems
* Cupferron **is genotoxic (KC1)** in experimental systems
* Crotonaldyhde **is electrophilic; is genotoxic; induces oxidative stress**; and **induces chronic inflammation (KCs 1, 2, 6)**
* Arecoline **is electrophilic**; **is genotoxic; alters DNA repair or causes genomic instability;** and **induces oxidative stress (KCs 1, 2, 3, 5)**

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Guidance from the US National Academies of Science

USING 21ST CENTURY SCIENCE TO IMPROVE RISK-RELATED EVALUATIONS

https://www.nap.edu/download/24635

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- The "[KCs] approach avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence."

- "The committee notes that key characteristics for other hazards, such as cardiovascular and reproductive toxicity, could be developed as a guide for evaluating the relationship between perturbations observed in assays, their potential to pose a hazard, and their contribution to risk."

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German Environment Agency

Umwelt Bundesamt

Use of Biomonitoring data in hazard and risk assessment of PFCs

Marike Kolossa-Gehring, André Conrad, Enrico Rucic, Aline Murawski, Rosa Lange, Jörg Wellmitz, Anja Duffek, Till Weber

German Environment Agency (Umweltbundesamt), Berlin/Dessau-Roßlau, Germany

1

Overview

Study design of ESB
Study design of GerES V

Results on PFOS, PFOA, PFHxS

- **Time trend in young adults**
- **Distribution of internal exposure in population**
- **Differences between subgroups**
- **Health assessment**

Conclusions and outlook

2

2

Monitoring in the ESB

non-representative sample of **20-29-year-olds in Germany, 1982-2021**

3

Monitoring in the ESB

non-representative sample of **20-29-year-olds in Germany, 1982-2021**

annual sampling at **4 locations**

approx. 120 healthy male and female Students (20 - 29 yrs.) in each city

No specific exposure / not representative

- **Urine** (24 hrs.)
- **Blood** (whole blood, plasma)

- **Self-administered questionnaire**
- **Dental anamnesis**

Cryo-archiving of samples: retrospective analyses

4

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6

Chemical analysis

ESB: 358 young adults (20-29 yrs.)
GerES V: Sub-sample of 1,109 children and adolescents (3-17yrs.)

PFAS analyzed in blood plasma by UHPLC-HRMS and LC-MS/MS.
LOQ ranged from 0.25 to 1 µg/L.

PFOS, PFOA, PFHxS, PFNA, PFDA,
PFBA, PFPeA, PFBS, PFHxA, PFHpA
PFUnA, PFDoDA…

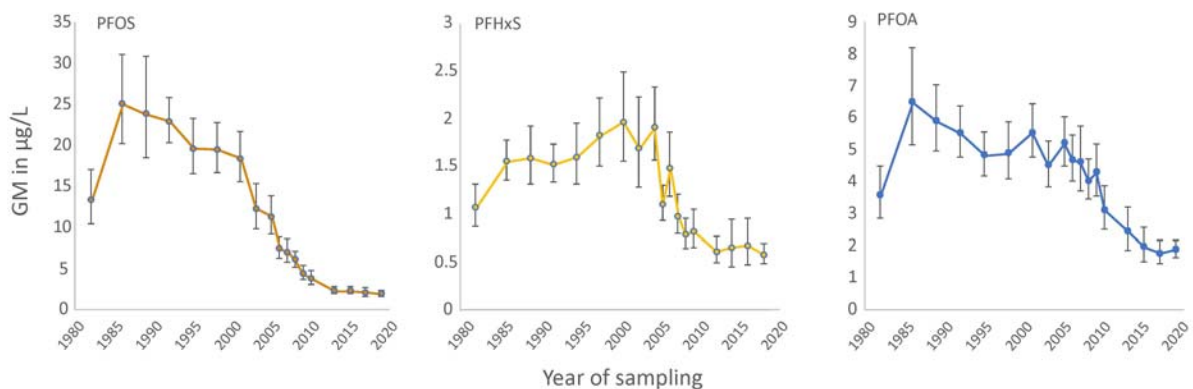Source: Fraunhofer IBMT

7

7

Time trend of PFOS, PFOA and PFHxS in young adults (20-29 yrs.)

8

8

4

Time trend of PFOS, PFOA and PFHxS in young adults (20-29 yrs.)
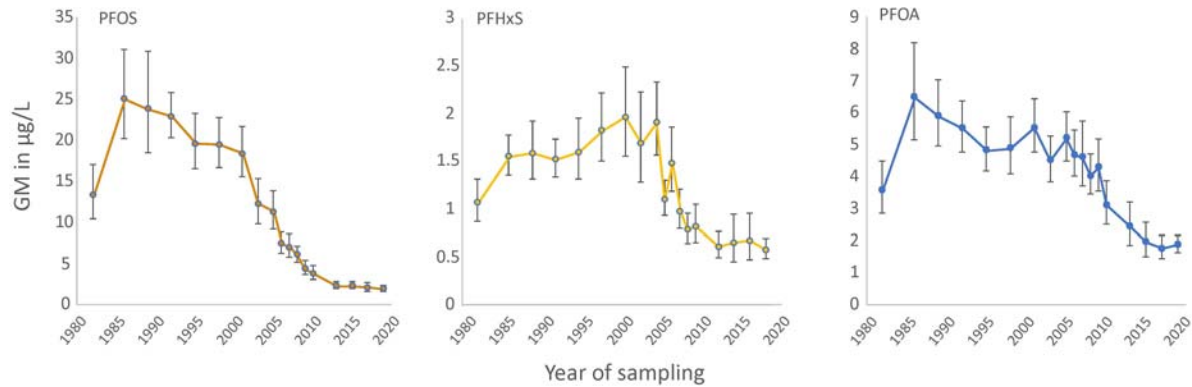
→ Decline in exposure for the three main PFAS

9

PFOS, PFOA and PFHxS in German children and adolescents (3-17 yrs.)

	LOQ	% ≥ LOQ	P50	P95	Max.	GM
PFOS	0.25	100	2.41	6.00	129	2.49
PFOA	0.50	86	1.27	3.24	6.33	1.12
PFHxS	0.25	74	0.38	1.26	34.1	0.36

in µg/L blood plasma

10

PFOS, PFOA and PFHxS in German children and adolescents (3-17 yrs.)

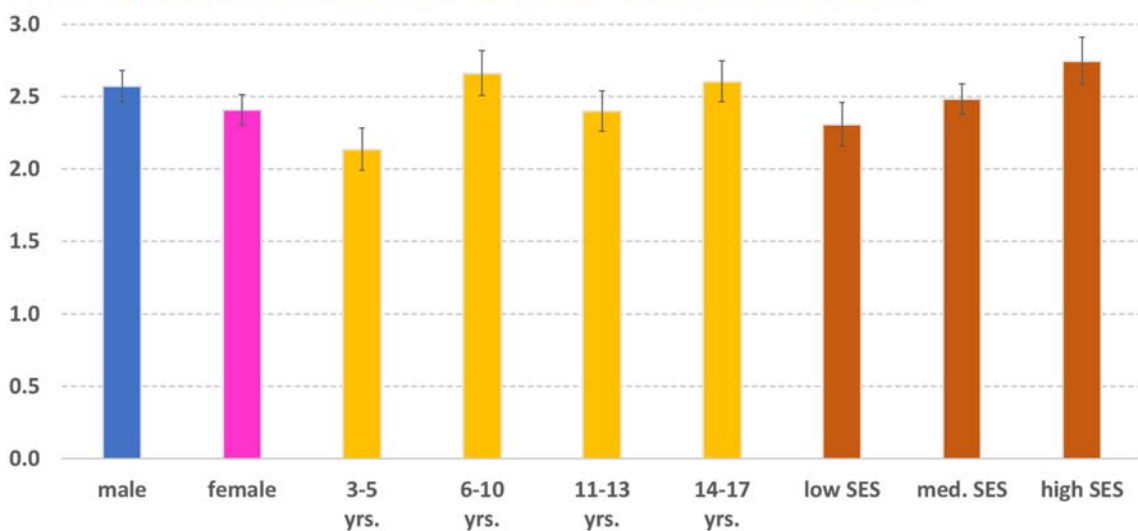|	LOQ	% ≥ LOQ	P50	P95	Max.	GM
PFOS	0.25	100	2.41	6.00	129	2.49
PFOA	0.50	86	1.27	3.24	6.33	1.12
PFHxS	0.25	74	0.38	1.26	34.1	0.36

in µg/L blood plasma

➡ HBM reference values for German children and adolescents

11

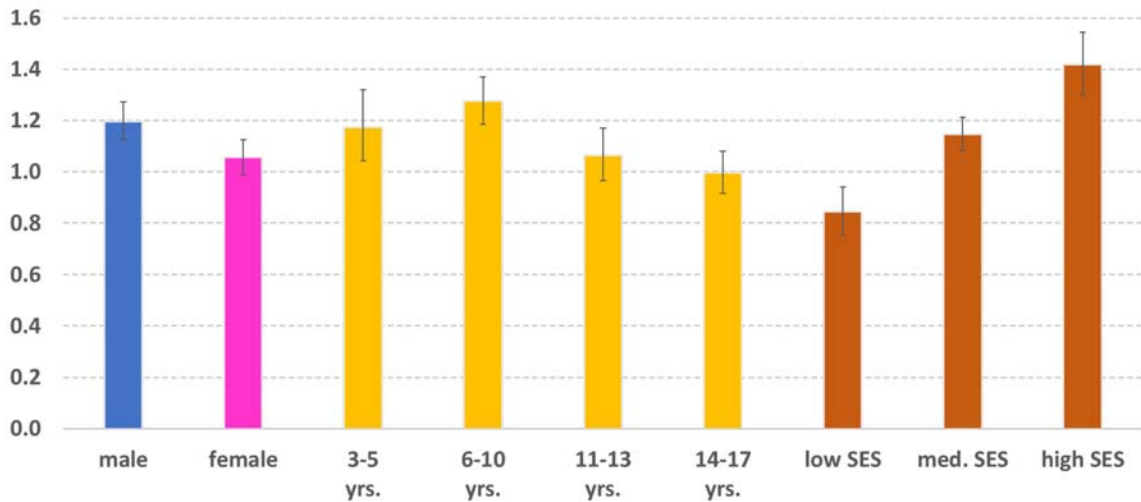
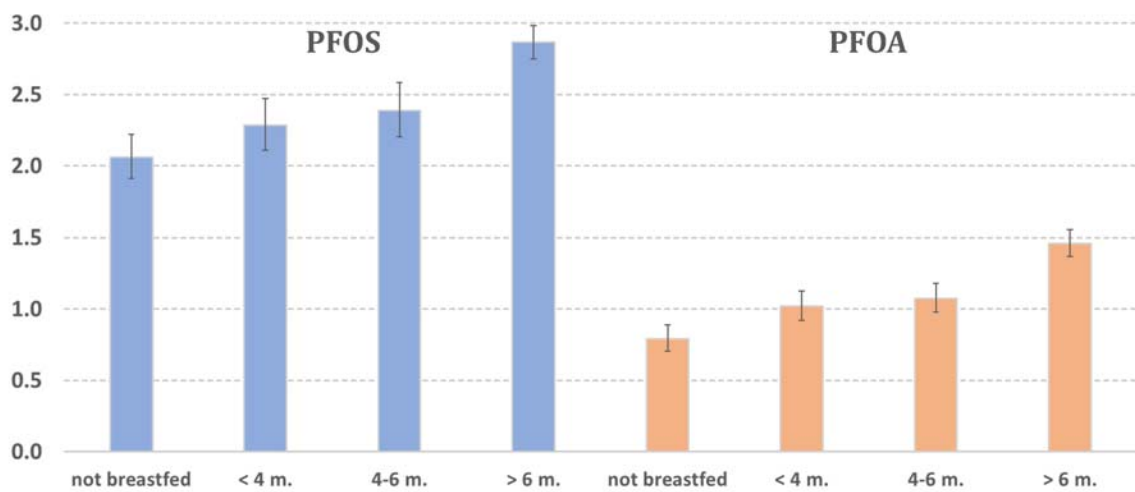## PFOS by socio-demographics (3-17 yrs., GM in µg/L)

12

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PFOA by socio-demographics (3-17 yrs., GM in µg/L)

13

PFOS, PFOA by duration of breastfeeding (3-17 yrs., GM in µg/L)

14

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Explorative linear regression analysis

	PFOS	
	β	p-value
Age (years)	↑ 0.135	**0.001**
Sex (male – female)	⬊ - 0.067	**0.025**
SES (low – medium – high)	→ 0.026	0.419
Total protein (g/L)	→ 0.027	0.405
BMI (kg/m²)	⬊ - 0.102	**0.008**
Duration of breastfeeding (months) (never – <4 – 4-6 – >6)	↑ 0.237	**0.000**

preliminary results

15

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Explorative linear regression analysis

	PFOS		PFOA	
	β	p-value	β	p-value
Age (years)	↑ **0.135**	**0.001**	→ - 0.025	0.507
Sex (male – female)	⬊ **- 0.067**	**0.025**	⬊ **- 0.078**	**0.008**
SES (low – medium – high)	→ 0.026	0.419	⬈ **0.067**	**0.032**
Total protein (g/L)	→ 0.027	0.405	→ - 0.043	0.172
BMI (kg/m²)	⬊ - 0.102	**0.008**	→ - 0.073	0.053
Duration of breastfeeding (months) (never – <4 – 4-6 – >6)	↑ **0.237**	**0.000**	↑ **0.273**	**0.000**

preliminary results

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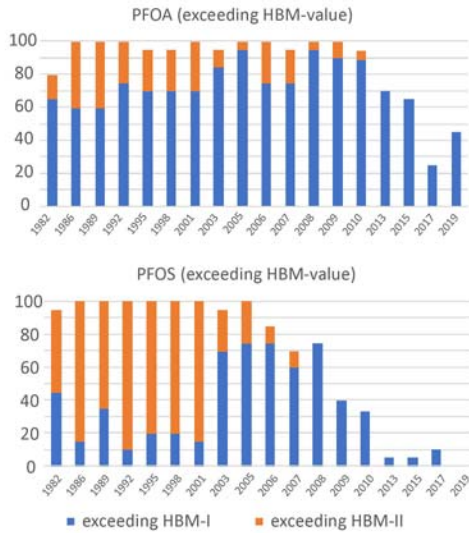
8

Health-based assessment of internal exposures (20-29 yrs.)

PFOA (exceeding HBM-value)

PFOS (exceeding HBM-value)

■ exceeding HBM-I   ■ exceeding HBM-II

	HBM-I	HBM-II
PFOA		
General Population	2 µg/L	10 µg/L
Women in childbearing age		5 µg/L
PFOS		
General Population	5 µg/L	20 µg/L
Women in childbearing age		10 µg/L

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Health-based assessment of internal exposures (20-29 yrs.)
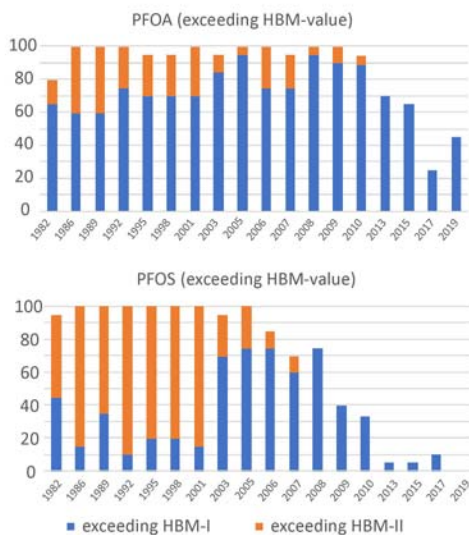
PFOA (exceeding HBM-value)

At or above **HBM-I-Value**: *adverse health effects cannot be ruled out with sufficient certainty*

PFOS (exceeding HBM-value)

■ exceeding HBM-I   ■ exceeding HBM-II

	HBM-I	HBM-II
PFOA		
General Population	2 µg/L	10 µg/L
Women in childbearing age		5 µg/L
PFOS		
General Population	5 µg/L	20 µg/L
Women in childbearing age		10 µg/L

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Health-based assessment of internal exposures (20-29 yrs.)

At or above **HBM-I-Value**: *adverse health effects cannot be ruled out with sufficient certainty*
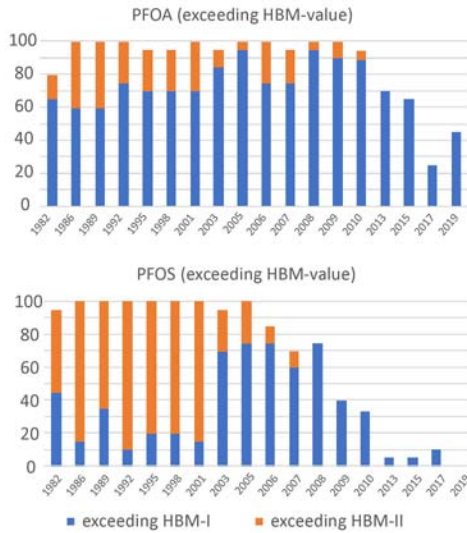
At or above **HBM-II-Value**: *adverse health effects are possible. Acute need for exposure reduction medical advice*

	HBM-I	HBM-II
PFOA		
General Population	2 µg/L	10 µg/L
Women in childbearing age		5 µg/L
PFOS		
General Population	5 µg/L	20 µg/L
Women in childbearing age		10 µg/L

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Health-based assessment of internal exposures – GerES (3-17 yrs.)

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Health-based assessment of internal exposures – GerES (3-17 yrs.)
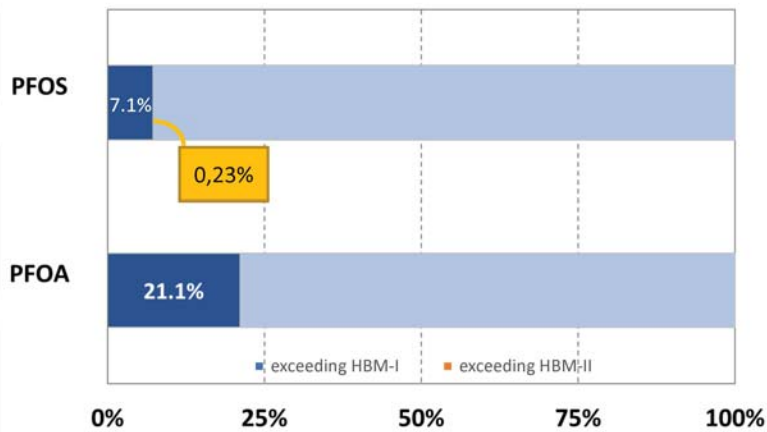
At or above **HBM-I-Value**: *adverse health effects cannot be ruled out with sufficient certainty*

PFOS — 7.1%, 0,23%
PFOA — 21.1%
exceeding HBM-I · exceeding HBM-II
0% 25% 50% 75% 100%

21

Health-based assessment of internal exposures – GerES (3-17 yrs.)

At or above **HBM-I-Value**: *adverse health effects cannot be ruled out with sufficient certainty*
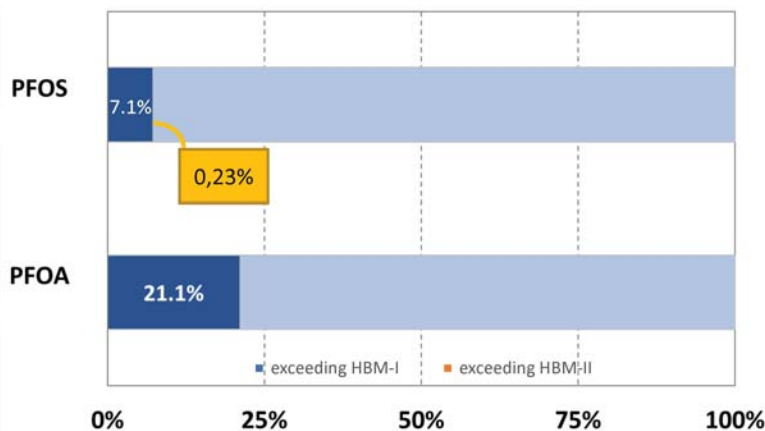
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0% 25% 50% 75% 100%
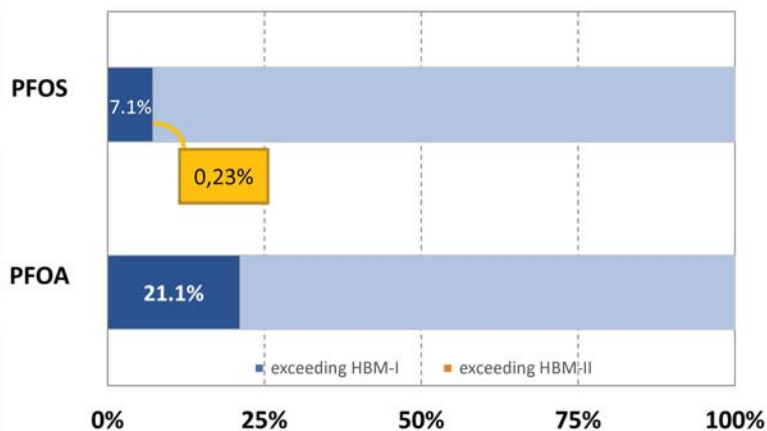
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Conclusions and outlook

ESB shows **clear declining trend** of the main PFAS (PFOA, PFOS, PFHxS)

GerES V provides **population-representative data on PFAS exposure** of German children and adolescents

For a considerable fraction of the young generation, PFOS and PFOA exposure raises concern, as **health effects can not be ruled out with sufficient certainty**

Next steps

- Further analysis of GerES V data for **identifying risk groups**
- Analysis of PFAS in GerES V **drinking water** samples
- Development of **communication strategy**

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Thank you very much for your attention.

We thank all participants, the Robert Koch Institute and Kantar Health for making GerES V possible.
Funding by the German Ministries for the Environment, Nature Conservation and Nuclear Safety (BMU) and of Education and Research (BMBF) is gratefully acknowledged.

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Umwelt
Bundesamt

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Comparison to NHANES (3-11 yrs., in µg/L)

Study	Type	Period	Sample: age and size	P50	P95	GM
PFOS						
GerES V, Germany	Plasma	2014-2017	3-11 years, N = 631	**2.34**	**6.43**	**2.43**
NHANES, USA	Serum	2013-2014	3-11 years, N = 639	**3.75**	**11.0**	**3.88**
PFOA						
GerES V, Germany	Plasma	2014-2017	3-11 years, N = 631	**1.37**	**3.50**	**1.25**
NHANES, USA	Serum	2013-2014	3-11 years, N = 639	**1.94**	**4.19**	**1.92**
PFHxS						
GerES V, Germany	Plasma	2014-2017	3-11 years, N = 631	**0.38**	**1.47**	**0.35**
NHANES, USA	Serum	2013-2014	3-11 years, N = 639	**0.81**	**2.14**	**0.84**

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Conducting Evaluations of Evidence that are Transparent, Timely and Lead to Health-Protective Actions

Some **Key Differences** in the ICNIRP and IARC Evaluations of **RF Evidence**

Professor James C. Lin, PhD
University of Illinois, Chicago
Email: lin@uic.edu

RSM London Feb 2021

1

What is ICNIRP

International Commission on Non-Ionizing Radiation Protection (1992)

Evaluate the state of knowledge about the effects of non-ionizing radiation (NIR) on human health

Provide advice on protection against harmful NIR effects

14 Members including Chair, Vice-Chair, plus a Sci Sec

WHO recognized NGO in Munich, Germany

ICNIRP functions as independent (PRIVATE) group

2

2

The International Agency for Research on Cancer (IARC)

IARC STAFF
Scientific work of IARC is organized into Research Sections and Groups.

Sections focus on particular areas of cancer research, while often collaborating closely on issues of common interest.

GOVERNANCE
WHO Agency, IARC follows the general governing rules of the UN.

Governed by its own Governing bodies: IARC Governing Council (GC) and IARC Scientific Council (SC).

IARC MEMBERSHIP
26 countries
IARC is the specialized cancer agency of
WHO (1965)

Objective of IARC is to promote international collaboration in cancer research and prevention.

LYON, FRANCE

3

3

IARC Monographs on Identification of Carcinogenic Hazards to Humans

- Identify environmental factors that can increase the risk of human cancer.

- Interdisciplinary Working Groups of expert scientists review published studies and evaluate evidence.

- RF RADIATION group of 31 scientists from 14 countries; Reviewed 100's articles.

- Classified RF (Including Mobile Phones) as 2B – "Possibly Carcinogenic" to Humans in 2011

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Key Differences in ICNIRP and IARC Evaluations

Reflected in publication on or treatment of human EPIDEMIOLOGY and ANIMAL RESEARCH

ICNIRP focus on RF tissue heating

A priori position leads to different decisions

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IARC v. ICNIRP Epidemiology of Cancer Risk

IARC decided a causal interpretation between exposure to mobile phone RF radiation and glioma or acoustic neuroma is possible for long term and heavy use > 15 yr & 3500 J/kg (Interphone + Hardell et al and Japanese).

ICNIRP concluded that within 10–15 years after the first use of mobile phones there is UNLIKELY to be a material increase in the risk of head cancer (gliomas - Interphone)

ICNIRP – Any increased risk was entirely explicable by various biases or design flaws, but Less Critical of Negative Reports

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PUBLISHED LIFE-LONG LAB RAT STUDIES

In 2011(2013), while classifying RF radiation as a 2B carcinogen, IARC suggested available scientific evidence was incomplete and limited, especially from animal experiments.

2018, two (US NTP; Italy 2018) RF studies showed consistent results in significant increased in total primary cancer or overall tumor rates in animal exposed life-long.

NTP: "Clear Evidence" 900 MHz RF radiation can lead to malignant schwannoma in the heart of male rats and "Some Evidence" for gliomas.

ICNIRP concludes the substantial limitations preclude conclusions being drawn concerning RF and carcinogenesis. Health Phys. 118(5):525–532; 2020

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WHY THE DIVERGENT EVALUATION OF THE SAME SCIENCE?
(IT'S THE HUMAN!)

Humans are not always rational or as transparent as advertised.

Scientists do not have the same level of knowledge or readily admit to that fact.

Scientists are not impervious to conflicts of interest, can be driven by egocentric motivations, or social preferences.

Established *A Priori* positions or values can lead to different decisions......think Stake-holders.

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Science Has Never Been Devoid of Politics

Nicolaus Copernicus, the 16th century Polish astronomer, set forth the revolutionary view that Earth revolved around the Sun.

HALF-CENTURY later, Galileo traveled to Rome to make the case in support of Copernicus through his new telescopic discoveries.

Galileo was condemned by the Holy Office of Inquisition of heresy and sentenced to imprisonment.

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Déjà vu. Nothing New !

◈ **There are Ample Examples From the History of Science**

The Brilliant Celebrated Nobel Laureate in Physics
Albert Einstein

Awarded for What Research Topic?

10

The Brilliant Celebrated Nobel Laureate Albert Einstein

What Research Topic? Theory of Relativity or E = mc²

Einstein's Nobel Prize in 1922, "for his services to theoretical physics, and especially for his discovery of the law of the photoelectric effect."

Pretty big deal today -- a minor contribution, at the time, the least accepted by the contemporary theoretical physicists.

Einstein was so renowned by that time, their failure to have awarded him the Prize had become an embarrassment.

So the selection was a political decision by the Nobel Committee.

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Thank You

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WHEN SCIENCE AND POLICY FAIL HIGH-RISKS COMMUNITIES: A CASE STUDY OF HEXAVALENT CHROMIUM

-Mark A. Mitchell MD, MPH, FACPM

National Medical Association (USA)

1

LOCATION

- Hartford, Connecticut
  - Northeastern U.S. city halfway between Boston and New York City
  - One of the lowest income cities in the U.S.
  - Capital city of one of the wealthiest states in the U.S.
  - Racial/Ethnic Demographics:
    - Population of 124,000
    - 81% non-White
    - Primarily Black and Latino

- Clay Arsenal Neighborhood
  - One of the lowest income neighborhoods in Hartford
  - High crime
  - Almost all non-White

2

PLINY STREET

- Densely populated block
- Fairly close-knit neighborhood
- Many families and children
- Very disinvested
- High crime
- Rental and Publicly supported housing
- Abandoned industrial building in middle of block

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SILEX BROWNFIELD SITE

- Former Proctor-Silex small appliance manufacturing facility located on this mostly-residential block
- Since their closure in the late 1960's/early 1970's many other small businesses opened and closed on the site.
- Only a shelter for homeless women and children survived on a part of the site
- The neighborhood wanted the abandoned blighted buildings razed
- The shelter wanted to expand, the neighborhood agreed

4

WHAT HAPPENED?

- In summer of 2010, the City of Hartford hired a contractor to demolish abandoned buildings
- On a Friday afternoon, the contractors breeched a concrete slab, and a yellow-green liquid came to the surface and spilled out.
- Contractors stopped work and notified the City
- It rained over the weekend and the liquid spread throughout the block
- On Monday, the City notified the state environmental agency
- The State came and spread 12 inches of clean soil on the site and covered it with a tarp, then called EPA

EPA RESPONSE

- Over the next several weeks
    - EPA tested the first 6 inches of clean soil
    - Retested site and found high levels of chromium VI and TCE
    - Retested to in an iterative manner to quantify and locate the areas of contaminated soil
    - Put up a fence around the site
    - Coordinated within EPA only, notified state environmental agency

- 3 Months later they issued a press release announcing a community meeting to explain their findings
- Community was outraged, the meeting went badly

COMMUNITY VERSION OF EVENTS

- Community finally convinced City to tear down blighted and dangerous buildings
- Work was begun, but stopped leaving piles of bricks on the site.
- After a month, someone showed up with a flatbed truck and agreed to pay cash to neighbors who would help clean and stack the bricks on the truck
- Several neighbors sat in puddles of yellow-green liquid cleaning the bricks
- Once the bricks were removed there was a concrete slab that made a perfect playground so the children didn't have to play in the street
- Parts of the fence were torn down and children brought their toys.

- Then the satellite TV reporters came and interviewed the mothers about what they thought of the highly contaminated property

WHAT HAPPENED NEXT

- Community did not trust City, State, or Federal gov't
- Got money from the City to hire their own trusted experts
- Assessment of EPA actions
  - EPA did not meet with community sooner because they wanted to be sure of results and have a remediation plan developed first
  - Afraid that community would not trust EPA if they did not have all the answers
  - Did not know to reach out to community leaders first
  - Were not willing to listen to community, since EPA was the expert
  - Were not coordinating meetings with other agencies, until requested
  - Would only test below the slab, not around the slab, due to funding limitations
  - Ignored community questions, although warned what to expect

HEALTH EFFECTS OF CHROMIUM VI

- Acute exposure
  - Inhalation: Lung irritation and sensitization
  - Direct contact: Skin irritation and painless ulcers that take months to heal

- Chronic exposure
  - Lung cancer

- Diagnosis difficult because Cr (VI) is converted by the body to Cr (III) which is non-toxic

9

ATSDR RESPONSE

- ATSDR delegated authority to the State health agency
- Health agency provided written info on Cr (VI) toxicity at community meetings
- Presumed that there was no possible exposure to Cr (VI)
  - Did not ask about possible exposures
  - Did not know about cleaning of bricks
- Did not coordinate with local health or other health agencies
- Were (reportedly) too scared to distribute health information or interview residents door-to-door
  - Did not ask whether people had symptoms
  - Did not investigate those with possible symptoms

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COMMUNITY FINDINGS

- Community distributed notifications and health information door-to-door
- Community consultant asked about, identified, and interviewed possible cases
- Community consultant found:
  - 5 people with exposure and symptoms
    - 6-year-old male from homeless shelter who admitted climbing fence in open-toed shoes, presenting with ulcer on foot remaining months after treatment with topical corticosteroid cream, but was not diagnosed by pediatrician with Cr (VI) toxicity
    - 23-year-old unemployed male who cleaned bricks barefoot in puddle of yellow-green liquid, complained of long-term ulcer between toes
    - 16-year-old autistic female with reported yellow-green liquid leaking into her basement
    - Elderly female with ulcers on her ankle who also cleaned bricks, died within one year
    - Elderly male with pre-existing circulatory problems in his legs who sat in puddle of liquids while cleaning bricks, died within one year

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ATSDR REJECTED COMMUNITY FINDINGS BECAUSE

- Claimed that the Cr (VI) concentration was too low to have acute health effects
  - Even though studies are not done in such high-risk populations (psychosocial stress)
- Asserted that if there really were people who had symptoms, they would have come to the community meetings and reported it to ATSDR
- State epidemiologists were not prepared to accept the diagnosis of Cr (VI) toxicity from the community environmental health physician over the diagnosis of conditions of unknown origin from patients' primary care physicians

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CONCLUSION

- The ATSDR report concluded that there we no possible acute health effects from this incident due to the NOEL concentration of chromium VI in healthy young White male workers
  - Even though there are probably no studies of Cr (VI) toxicity levels in six-year-olds, in high poverty populations, in teens with autism, or in elderly populations with pre-existing circulatory conditions.
- In my experience, this is typical of ATSDR reports that conclude no effect by design
  - When there is real data showing health effects in high-risk populations, they reject it because standard data or models in dissimilar populations shows no effect. The standard data is assumed to be applicable.
  - They will not (cannot?) incorporate real data into their models, no matter how dissimilar it is to the theoretical or historical data.
- Note: the property was eventually remediated and the shelter did expand

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Evidence-to-decision frameworks: a landscape analysis

SL Norris

11 February 2021

SL Norris Declarations of Interests

- Member GRADE Working Group (2001 - present)
- Co-Project Manager (at WHO): INTEGRATE (2017-2019)
- Contractor UCSF (Dr Chartres and Woodruff((2020-2021)
- Stock in several chemical companies (information available upon request)

2

Evidence-to-decision frameworks

- Provide a structured and transparent approach for decision-makers to use when developing recommendations or making decisions
- Include explicit criteria which decision-makers consider individually and in aggregate
- Facilitate:
  - consideration of all relevant criteria in the decision-making process
  - examination of the pros and cons of each intervention option
  - presentation of relevant evidence for each criterion
  - identification of the reasons for any disagreement across decision-makers
  - transparent reporting of the decision-making process
  - crafting of the rationale statement for each recommendation
  - implementation in the local context

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Evidence-to-decision frameworks

- Terminology varies
  - Clinical medicine and public health: "evidence-to-decision" or "evidence-to-recommendation" FW or criteria
  - HTA: "multicriteria decision analysis (MCDA)", "structured deliberation", "value assessment framework"

- Decision-making is complex: contextual factors; individual decision-maker's characteristics, emotions, experiences

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Objectives of the landscape analysis

1. Identify key EtD FWs in clinical medicine, public health, environmental health
2. Compare and contrast the EtD criteria
3. Outline next steps for developing an EtD FW for environmental health

Purpose: to inform development of a EtD FW to guide decision-making related to interventions for: 1) mitigating harmful effects of exposures; or 2) preventing exposure or harmful outcomes

Focus of this analysis:
- Questions of intervention benefits/harms
  - Not other types of questions (eg risk assessment, setting of target values)
- Substantive EtD criteria
  - Not the *processes* for decision-making or formulation of recommendations
  - Not the assessment of individual studies or the quality/certainty of a body of evidence

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Methods

- Organizations
  - Convenience sample, focus on EH organizations

- Review of reviews of FWs
  - Search PubMed: [policy-making OR decision-making] AND [template OR tool OR framework}"
  - Filters: "systematic reviews", 10 years

6

Results: Organizations

- Examined 14 organizations
- GRADE: 1 organization/5 frameworks
- Sponsor: national gov't (n=5), WHO (2), state gov't (1), NGO/academia (5)
- Focus
  - Clinical guidelines: USPSTF, SIGN
  - Public health decision-making: ACIP (CDC), GCPS (CDC) , NICE (UK), WHO, INTEGRATE
  - Environmental health: BCPP, CalEPA, Navigation Guide
  - HTA: EVIDEM, ICER, ISPOR
- Development methods
  - Similar across most FWs: expert group, iterative, examine other org's FWs
  - Most comprehensive: INTEGRATE
  - Mostly developed by topic experts; GRADE and INTEGRATE had diverse groups

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Results: Evidence-to-decision considerations for selected organizations
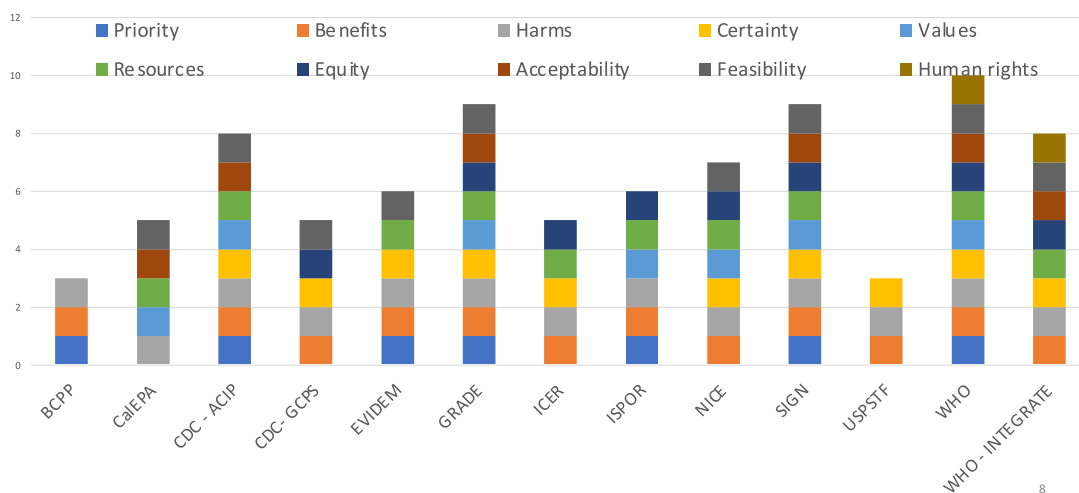
8

Results: evidence-to-decision considerations for selected organizations, continued

N=14 (GRADE as 1 FW)

Use evidence to inform the considerations: 14

Specific criteria:
- Harms: 14
- Benefits: 12 (not CalEPA or Nav Guide)
- Quality/certainty of the evidence on benefits and harms: 11 (not CalEPA, CA BCPP, ISPOR)
- Resource use or CE: 11
- Feasibility: 9
- Equity: 8
- Values: 7
- Priority of the problem: 7
- Acceptability/preferences: 6
- Human rights: 2 (WHO, INTEGRATE)

- Variability in terminology, categories/main criteria vs sub-criteria
  - eg values and preferences; resource use

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GRADE evidence-to-decision frameworks

- Alonso-Coello *BMJ* 2016
- 5 basic FWs:
  - clinical recommendations – individual perspective
  - clinical recommendations - population perspective
  - coverage decisions
  - health system and public health recommendations/decisions
  - diagnostic, screening and other screening tests
- All fundamentally the same
  - N=12 criteria
  - Public health:
    - "Option" may be preferable to "intervention"
    - Resources may be more important than in the clinical FW
    - Equity, acceptability and feasibility are likely more important

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Evidence-to-decision frameworks based on GRADE

- Scottish Intercollegiate Guideline Network (SIGN)
- UK National Institute of Health and Care Excellence (NICE)
- US CDC Advisory Committee on Immunization Practices (ACIP)
- WHO (Handbook 2014)

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Other evidence-to-decision frameworks

- WHO INTEGRATE (2019)
  - Developed in response to a need to take a complexity perspective and to incorporate public health and WHO-specific values when developing WHO guidelines
  - Based on systematic review of decision criteria in health and theoretical FW
  - Broad focus:
    - Move beyond benefits and harms
    - Examine the specific context in which interventions are delivered
    - Include social and economic determinants of health
  - Consider EtD criteria at planning stage of guideline development: which criteria are critical for decision-making? For which criteria is evidence needed?
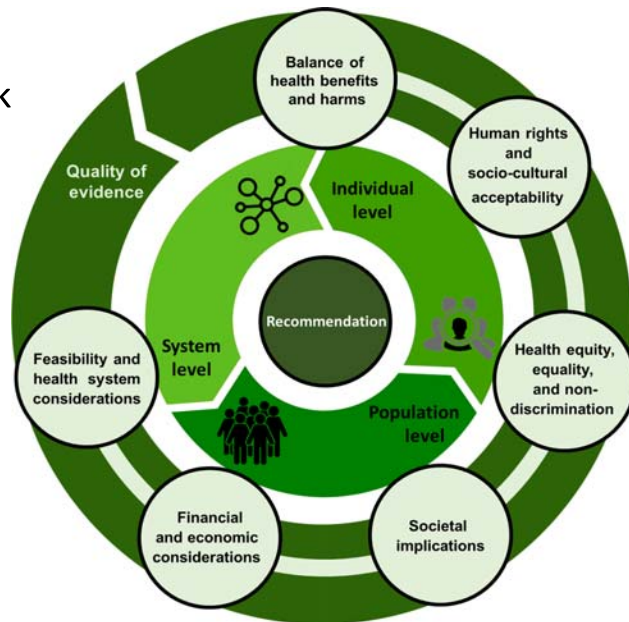 - Advocate for use of logic models or conceptual FW

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WHO-INTEGRATE

Evidence-to-decision framework

Rehfuess et al. 2019

6 domains, with sub-criteria

Health equity, equality and non-discrimination
- distribution of benefits and harms
- affordability
- accessibility
- severity and/or rarity of the condition
- lack of a suitable alternative

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Environmental health organizations which have EtD criteria/framework for recommendations on interventions

1. **CalEPA**
   - Risk management approach for pesticides (2017):
     1. Deciding whether the proposed or current use of a pesticide results in an unacceptable risk.
     2. Identifying options to minimize those risks.
     3. Evaluating those options according to a value system that includes scientific, social, legal and economic factors, as well as practicality and enforceability.
     4. Selecting an effective course of action to reduce or eliminate unacceptable health or environmental risks.

2. **California Breast Cancer Prevention Partners (BCPP)**

   Interventions which address BrCA risk and protective factors were prioritized according to criteria:
   - Does the intervention support the science-based intervention goals?
   - Is the intervention in alignment with the Guiding Principles of *Paths to Prevention*?
   - Is there evidence that the intervention has been successful in the past… or does it show potential for success…?
   - Does the intervention address cross-cutting, systemic problems?
   - Was there general agreement that the intervention would do no harm…?

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Environmental health organizations which have EtD criteria/framework for recommendations on interventions

3. Program of Reproductive Health and the Environment (PRHE)
   - Navigation Guide, recommendations for prevention:
     - Risk assessment combined with consideration of: 1) whether a less toxic agent is available as an alternative; 2) "values and preferences"; 3) costs; and 4) certainty of evidence and to arrive at a recommendation (strong or discretionary) (Woodruff et al. 2011 Health Affairs)
   - Currently working to advance this FW

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Study limitations

Limitations in the approach
- Convenience sample of organizations/FWs
- Review: limited search strategy, review of reviews, individual FWs not examined

Limitations in the available data
- Sparse descriptions of FW development methods
- Variable terminology – made comparisons difficult (eg "values and preferences")

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Steps for developing an EtD framework or adapting an existing one

ETD FRAMEWORK
DEVELOPMENT PROCESS

1. REVIEW EXISTING FRAMEWORKS
2. DEFINE PRINCIPLES
3. IDENTIFY TYPES OF QUESTIONS
4. SELECT EXISTING FRAMEWORK
5. MODIFY FRAMEWORK
6. PILOT TEST & REVISE
7. EVALUATE & MODIFY

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Principles underpinning decision-making on interventions in environmental health

Define a set of guiding principles for decision-making

Did not find good examples

Types of principles
1. Principles for process of decision making
   a. eg, inclusivity – stakeholder involvement
   b. Transparency; explicit rationale for decisions, etc.
2. Principles underpinning the substance of the recommendations/decisions
   a. eg, based on the best available evidence
   b. precautionary principle, etc.

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Key issues when developing/adapting an evidence-to-decision framework in environmental health

- Most FWs focus on single-component interventions and linear causal pathways, and don't consider the context (ie don't take a complexity perspective)
- Need to be strategic and parsimonious about which criteria to include and when to collect evidence
- Involve diverse stakeholders: EH (epi, tox, policy-makers), social scientists, social justice/human rights/ethics, expertise in vulnerable populations, economics, implementation, regulatory
- Need to be explicit as to the purpose of the FW: types of questions/decisions; perspective (societal, national, etc.)

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Recommendations for developing an EtD

Step 4. Select existing FW

Step 5. Modify FW

- GRADE is dominant and useful starting point
- Need to augment criteria for societal implications and human rights/ ethics/justice
  - Consider sub-criteria, eg INTEGRATE
- Need clear definitions and optimal terminology

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Conclusions

- EtD are a useful tool for decision-making
- Key domains for decision-making are common across FWs examined
  1. Priority of the problem
  2. Benefits and harms, and their balance
  3. Quality of the evidence on benefits and harms
  4. Resource considerations
  5. Equity
  6. Values
  7. Feasibility
  8. Acceptability/preferences
  9. Human rights

- Variability in: terminology, categorization, emphasis, sub-questions/domains
- Steps for developing/adapting an EtD FW
  - Define set of principles which will underpin process and criteria
  - Diverse input
- FW will evolve with use/testing

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Decision-Making Under Uncertainty and Ignorance
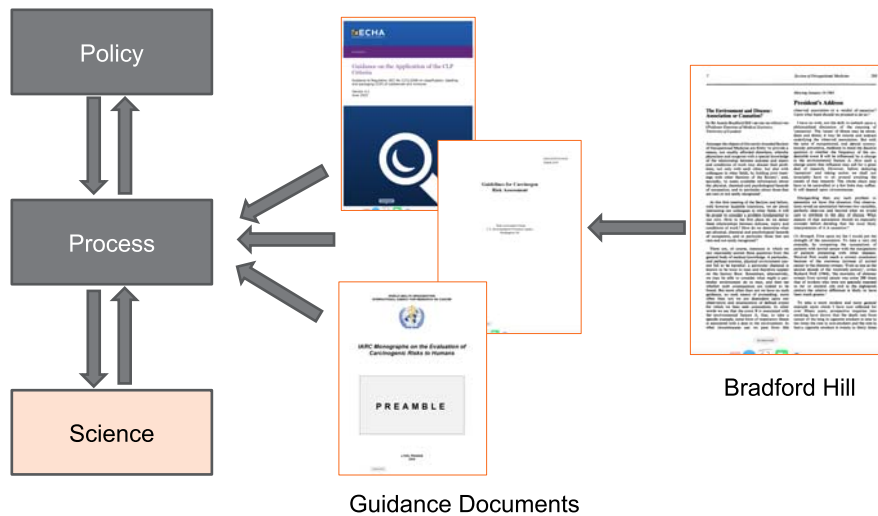
Christopher J. Portier, Ph.D.

February 8, 2021

Workshop on Conducting Evaluations of Evidence that are Transparent, Timely and Lead to Health-Protective Actions.

Online, Feb 8-11, 2021

1

1

Policy, Process and Science

Bradford Hill

Guidance Documents

2

2

What is uncertainty?

- Scientific uncertainty
  - Lack of mechanistic understanding
- Statistical uncertainty
  - Noise exceeds signal
- Process uncertainty
  - Clarity of purpose
  - Unclear logic leading to regulatory decision
- Synonyms (Merriam-Webster Dictionary)
  - distrust, doubt, dubiety, incertitude, misgiving, mistrust, query, reservation, skepticism, suspicion

3

3

Reducing Uncertainty, Improving Transparency

- Guidelines
  - Establish rules for scientific evidence and its use
  - Avoid developing rules "on the fly" for a specific agent under review
- Science Policy
  - Establish rules for areas where scientific data provides limited guidance
    - Public-health protective or precautionary
    - Minimal data for "safety"
    - Extrapolation
      - Dose
      - Species
- Process
  - Who, what, when

4

4

Ignorance in Decision-Making

- Lack of knowledge, education or awareness
- Science
  - Data gaps (lack of knowledge)
    - Formal versus informal imputation
  - Rapid advances (lack of education)
    - How to use newest science in decision-making
    - Lack of formal guidance
  - Hidden in plain sight (lack of awareness)
    - Provide reams of data on paper
    - Minimal acceptable analysis

5

5

Example

- Glyphosate
  - Association with NHL in humans
  - Causes malignant lymphomas in male and female CD-1 mice
    - Males (2 +, 1 +/-, 1 -), females (2+, 3 -), pooled analyses +
  - Genetic Models in Mice (*Wang et al., 2019, J. Hematol. Onc.*)
    - Increase in M-spike in gene-dependent manner in homozygous and heterozygous male and female Vk*MYC mice but not in null mice
    - Activation-induced cytidine deaminase (AID) induced in gene-dependent and dose-dependent manner in homozygous and heterozygous male and female Vk*MYC mice but not in null mice
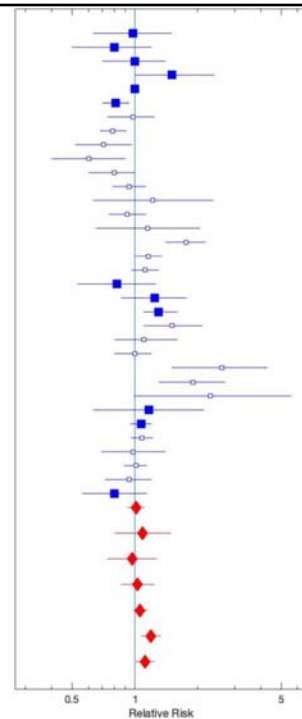
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Example

- Radiofrequency Electric and Magnetic Fields
    - Associated with gliomas and acoustic neuromas in humans
    - NTP study gliomas, heart Schwannomas
    - Anderson et al. (2004)
        - F-344 rats, in-utero exposure, 1620 MHz, head only
        - Oligodentroglioma in males 0/90, 1/90, 2/90, p_{trend}=0.147
            - Historical control range 0% to 2%
            - 20 controls with ~0/50, 1 with 1/50
   - Formal test with HC p_{Tarone}<0.001

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Example:
RF-EMF Meta-Analysis
Ever vs Never Exposure

Study	RR	Lower	Upper
A: Hardell et al. (1999) [1994-1996]	0.98	0.63	1.50
B: Muscat et al. (2000) [1994-1998]	0.80	0.50	1.20
C: Inskip et al. (2001) [1994-1998]	1.00	0.70	1.40
D: Auvinen et al. (2002) [1996]	1.50	1.00	2.40
E: Gousias et al. (2009) [2005-2007]	1.00	0.99	1.01
F: INTERPHONE (2010) [2000-2004]	0.81	0.70	0.94
F1: Schuz et al. (2006) [2000-2003]	0.98	0.74	1.24
F3: Lahkola et al. (2007) [2000-2004]	0.78	0.68	0.91
F3a: Christenson et al. (2005) [2000-2002]	0.71	0.52	0.97
F3b: Klaeboe et al. (2007) [2001-2002]	0.60	0.40	0.90
F3c: Lonn et al. (2005) [2000-2002]	0.80	0.60	1.00
F3d: Hepworth et al. (2006) [2000-2004]	0.94	0.78	1.13
F4: Takebayashi et al. (2008)	1.22	0.63	2.37
F5: Cardis et al. (2011) [2000-2004]	0.92	0.75	1.13
F5a: Hours et al. (2007) [2001-2003]	1.15	0.65	2.05
F6: Referent 1-1.9 years (meta)	1.75	1.40	2.18
F7: Referent <5 hours use (meta)	1.16	1.00	1.35
F8: Referent <150 calls (meta)	1.12	0.96	1.30
G: Baldi et al. (2011) [1999-2001]	0.82	0.53	1.26
H: Coureau et al. (2014) [2004-2006]	1.24	0.86	1.77
I: Hardell et al. (2015) [1997-2003, 2007-2009]	1.30	1.10	1.60
I1: Hardell et al. (2006) [1997-2003]	1.50	1.10	2.10
I1a1: Hardell et al. (2002) [1997-2000] Analog	1.10	0.80	1.60
I1a2: Hardell et al. (2002) [1997-2000] Digital	1.00	0.80	1.20
I1b1: Hardell et al. (2006) [2000-2003] Analog	2.60	1.50	4.30
I1b2: Hardell et al. (2006) [2000-2003] Digital	1.90	1.30	2.70
I2: Hardell et al. (2013) [2007-2009]	2.30	0.99	5.60
J: Yoon et al. (2015) [2002-2007]	1.17	0.63	2.14
K: Frei et al. (2011) [1990-1995, end 2007] meta	1.07	0.95	1.20
K1: Frei et al. (2011) Males	1.08	0.96	1.22
K2: Frei et al. (2011) Females	0.98	0.86	1.40
K3: Schuz et al. (2006) [1987-1995, end 2002]	1.01	0.89	1.14
K4:Johansen et al. (2001) [1987-1995, end 1996]	0.94	0.72	1.20
L: Benson et al. (2013) [1999-2005, follow-up 2009]	0.80	0.56	1.14
Meta Analysis A,B,C,D,E,F,G,H,I,J,K,L Homogeneity Test: I^2=55.84 p=0.01	1.01	0.92	1.11
Meta Analysis F,H,I,J Homogeneity Test: I^2=82.35 p=0.00	1.09	0.80	1.49
Meta Analysis K,L Homogeneity Test: I^2=58.91 p=0.84	0.97	0.74	1.27
Meta Analysis F,H,I,J,K,L Homogeneity Test: I^2=74.48 p=0.00	1.03	0.86	1.24
Meta Analysis A,B,C,D,E,F8,G,H,I,J,K,L Homogeneity Test: I^2=42.40 p=0.15	1.06	0.98	1.15
Meta Analysis F8,H,I,J Homogeneity Test: I^2=0.00 p=0.68	1.19	1.07	1.33
Meta Analysis F8,H,I,J,K,L Homogeneity Test: I^2=26.13 p=0.24	1.12	1.01	1.24

8

4

Example:
RF-EMF Meta-Analysis
Years of Use
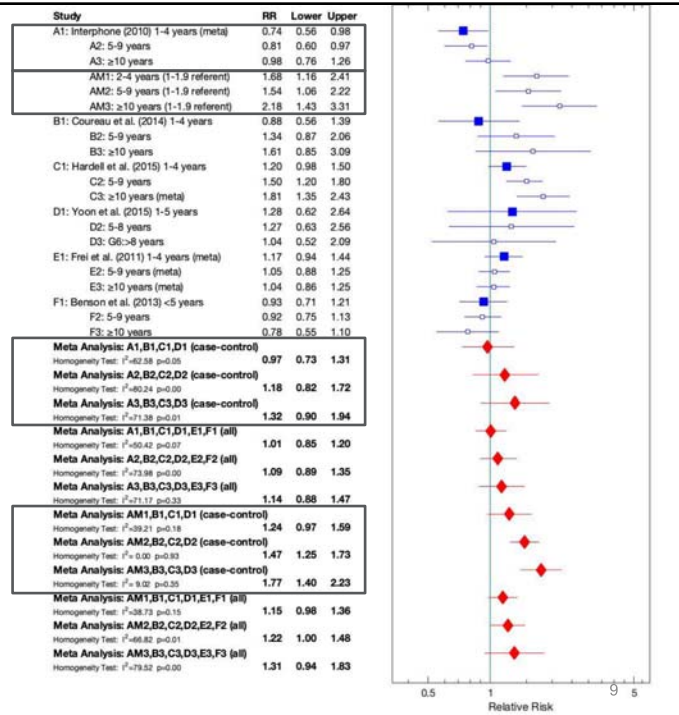
9

Meta Regression Studies[a,b]	Coefficient	P>|Z|	95% Confidence Interval		I²	pQ
All	1.007	0.004	1.002	1.012	68.18	<0.001
drop Inskip et al. (2001)	1.007	0.004	1.002	1.012	71.34	<0.001
drop Interphone (2010)	1.011	<0.001	1.005	1.017	54.36	0.006
drop Coureau et al. (2014)	1.006	0.02	1.001	1.011	71.65	<0.001
drop Hardell et al. (2015)	1.004	0.184	0.998	1.010	61.27	0.001
drop Yoon et al. (2015)	1.008	0.001	1.003	1.013	69.85	<0.001
Meta Regression Studies[a,b]	Coefficient	P>|Z|	95% Confidence Interval		I²	pQ
All	1.010	<0.001	1.006	1.014	33.95	0.054
drop Inskip et al. (2001)	1.010	<0.001	1.006	1.014	38.66	0.037
drop Interphone (2010)	1.011	<0.001	1.005	1.017	54.36	0.006
drop Coureau et al. (2014)	1.009	<0.001	1.005	1.013	35.34	0.065
drop Hardell et al. (2015)	1.008	0.003	1.003	1.013	0.49	0.451
drop Yoon et al. (2015)	1.011	<0.001	1.007	1.014	27.65	0.118

a – studies included in the analysis are Inskip et al. (2001), Interphone (2010), Coureau et al. (2014), Hardell et al. (2015), Yoon et al. (2015)

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5

Major Issues For Reducing the impacts of Uncertainty and Ignorance In Decision-Making

- Have clear policy guidance and follow it (e.g. precautionary principle)
- Develop guidelines at all levels and follow them
- Do not force science to make policy decisions
  - EU pesticides and cancer hazard
- Force consistency in analyses and ,where possible, conduct re-analyses
  - Avoid using least powerful analysis methods
- Avoid ad-hoc analyses, use formal methods of analysis
  - Avoid the use of ad-hoc, dogmatic methods to address testable hypotheses
  - Encourage use of pooled analyses, met-analyses, etc.
- In weight-of-evidence, provide clear logical explanation for decisions
  - Do not down-weigh peer-reviewed studies vs. regulatory studies
  - Do not ignore or over-interpret novel models/methods (science advisors)
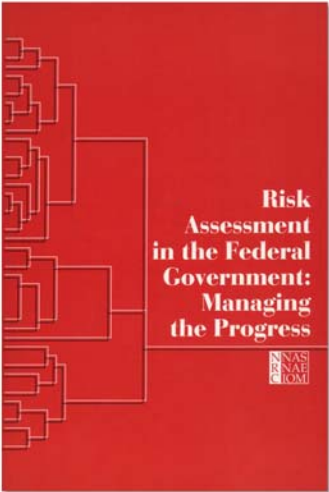 - Avoid judging one paper at a time (Can't see the forest, focused on trees)

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21st century approach to risk assessment

Hazard   Exposure   Dose Response   Risk Management
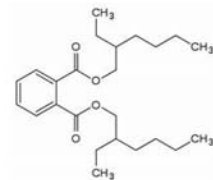
months - years
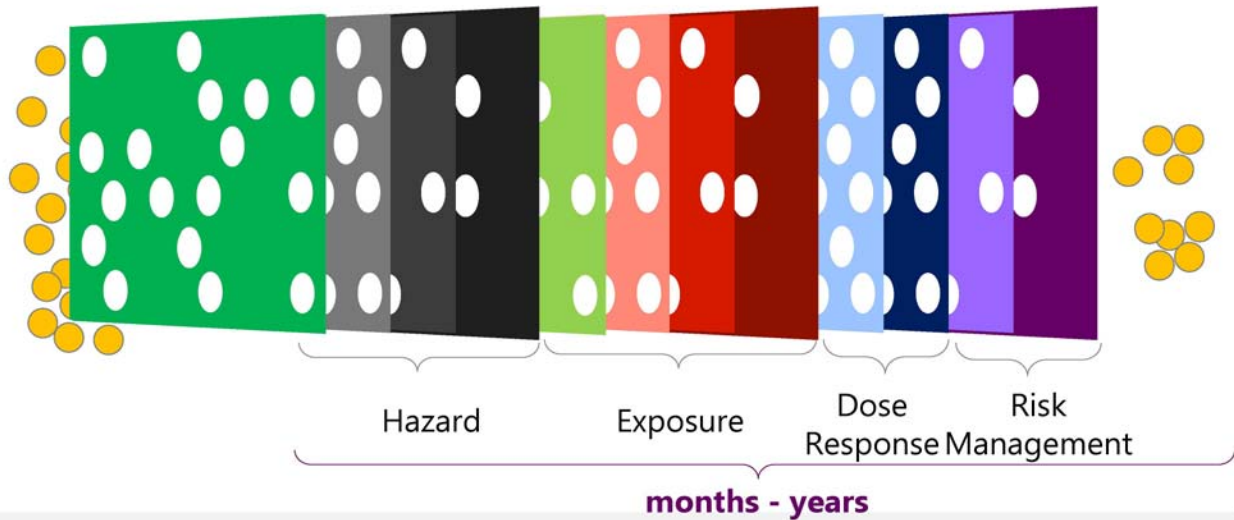
5

Case Study Example: Di(2-ethylhexyl)phthalate (DEHP)

Member of the phthalate family of chemicals - added to some plastics to make them flexible

Found in a variety of consumer products, including flooring, wall coverings, upholstery, lunch boxes, food packaging materials, surgical equipment

Present in dust samples across the U.S. and in people

Approx. concentration(ng/g)

250,000   5,000   1,000   500   100

DEHP------------DEHA-DIBP-------DEP-DCHP-------------------------DMP

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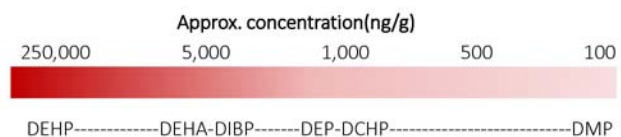
Whole animal studies and authoritative bodies classify DEHP as toxic to endocrine and reproductive systems

Candidate Chemical and/or Group Name	ToxRefDB	Endocrine Tox	Reproductive Tox
Dibutyl phthalate (DBP)	■	■	■
Butylbenzyl phthalate (BBP)	■	■	■
Diisobutyl phthalate (DIBP)			■
Di-n-pentyl phthalate			■
Dicyclohexyl phthalate (DCHP)	■	■	■
Di-n-hexyl phthalate (DnHP)			■
Mono-n-butyl phthalate (MnBP)		■	■
Di(2-ethylhexyl)phthalate (DEHP)	■	■	■
Diethyl phthalate (DEP)	■	■	■
Dimethyl phthalate (DMP)		■	■

DEHP has endocrine relevant active hit calls in ToxCast
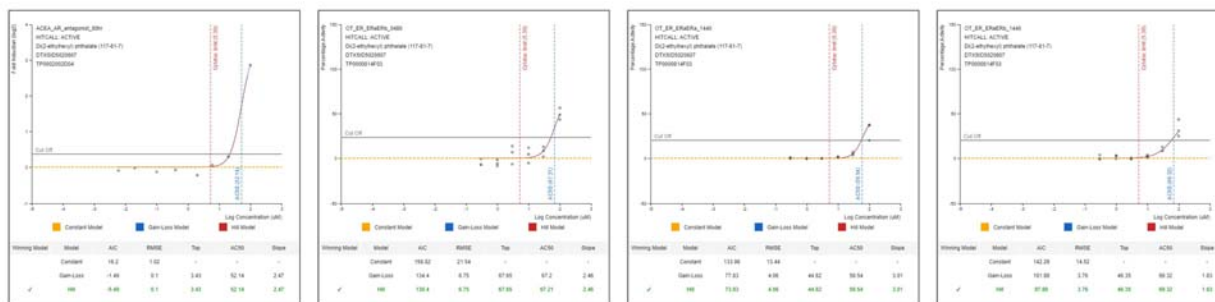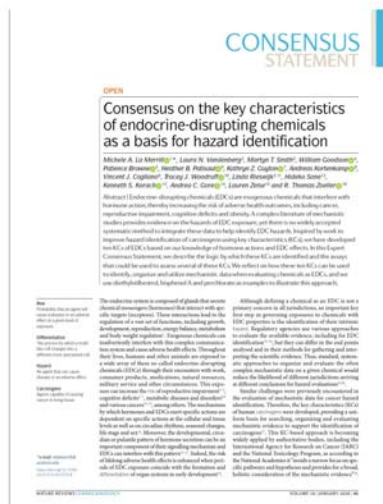

Androgen Receptor

Estrogen Receptor

DEHP has 3 of the Key Characteristics of EDCs

Key Characteristic	DEHP
KC1 Interacts with or activates hormone receptors	
KC2 Antagonizes hormone receptors	
KC3 Alters hormone receptor expression	✓
KC4 Alters signal transduction in hormone responsive cells	
KC5 Induces epigenetic modifications in hormone-producing or hormone-responsive cells	✓
KC6 Alters hormone synthesis	✓
KC7 Alters hormone transport across membranes	
KC 8 Alters hormone disruption or circulating hormone levels	
KC9 Alters hormone metabolism or clearance	
KC10 Alters fate of hormone-producing or hormone-responsive cells	

La Merrill, Michele A., Laura N. Vandenberg, Martyn T. Smith, William Goodson, Patience Browne, Heather B. Patisaul, Kathryn Z. Guyton, et al. "Consensus on the Key Characteristics of Endocrine-Disrupting Chemicals as a Basis for Hazard Identification." *Nature Reviews. Endocrinology* 16, no. 1 (2020): 45–57. https://doi.org/10.1038/s41574-019-0273-8.

9

Correlations with locations of DEHP emitting facilities and race/language spoken and multi-unit housing
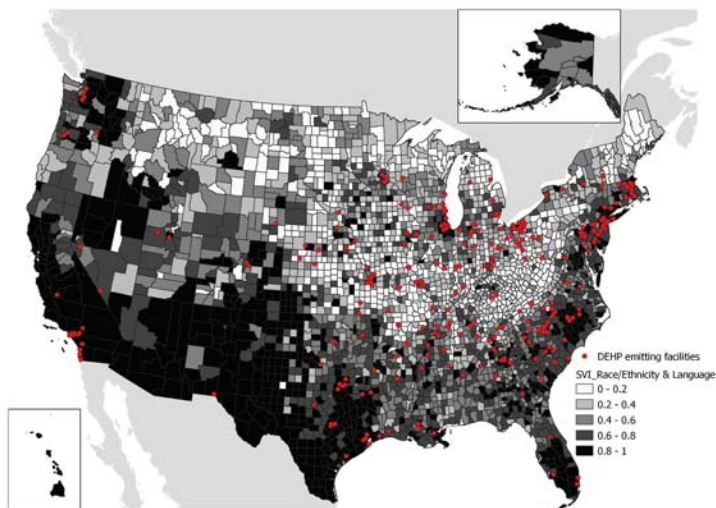
Crowded Housing

Minority Status & Language

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Should DEHP be a chemical of significant concern?

Evidence	DEHP
Endocrine active in animal models	✓
Endocrine active on authoritative lists	✓
Endocrine active in ToxCast	✓
Endocrine active using Key Characteristics	✓
Present in the products, the environment, and/or biosampling	✓✓✓
Potential for disproportionate exposures/Environmental Justice concerns	✓

11

DEHP has endocrine relevant active hit calls in ToxCast

Androgen Receptor → 1 out of 6 assays

Estrogen Receptor → 3 out of 16-18 assays

12

6

ER Model figure from Integrated Bioactivity and Exposure Ranking Approach – USEPA FIFRA SAP December 2 - 5

13

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16

Our value structures can influence the ways we generate and interpret data

New tools and applications should:
- Maximize public health protections
  - Minimize false negatives
  - Permit higher levels of false positives.
- Ensure protections against perpetuating or amplifying health disparities.
- Be used in the most appropriate decision contexts

Ginsberg, Gary L., Kristi Pullen Fedinick, Gina M. Solomon, Kevin C. Elliott, John J. Vandenberg, Stan Barone, and John R. Bucher. "New Toxicology Tools and the Emerging Paradigm Shift in Environmental Health Decision-Making." *Environmental Health Perspectives* 127, no. 12 (December 2019): 125002. https://doi.org/10.1289/EHP4745.

17

Should DEHP be a chemical of significant concern?

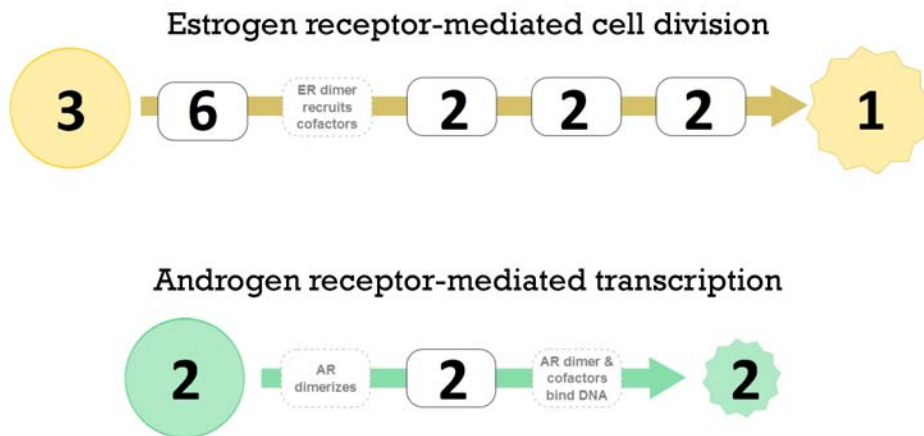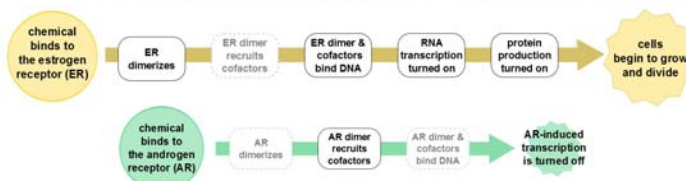| Evidence	DEHP
Endocrine active in animal models	✔
Endocrine active on authoritative lists	✔
Endocrine active in ToxCast	✔
Endocrine active using Key Characteristics	✔
Present in the products, the environment, and/or biosampling	✔✔✔
Potential for disproportionate exposures/Environmental Justice concerns	✔

18

Thank you!

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Future applications of the key characteristics approach

https://keycharacteristics.org

Martyn Smith
School of Public Health,
University of California, Berkeley CA, USA

martynts@berkeley.edu   http://superfund.berkeley.edu

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1

Summary of today's talk

- Mechanistic data plays an increasingly important role in hazard identification

- The key characteristics (KCs) provide the basis for a knowledge-based, objective approach to interpreting mechanistic data that contrasts with the reductive and problematic MOA/AOP approach

- Recent IARC, EPA, CalEPA and NTP evaluations have illustrated the utility of the KC approach

- Key characteristics for reproductive toxicants, endocrine and metabolic disruptors, neurotoxicants, cardiovascular toxicants, immunotoxicants and hepatotoxicants have or are being developed

2

2

Need KCs for Evidence Integration in Identifying Chemical Hazards

- Human studies – epidemiology
- Animal studies – usually in rodents –acute, subchronic and chronic studies
- In vitro studies – e.g. HTS: Tox21/Toxcast
- Mechanistic data in humans (biomarkers), animals, in vitro and in silico – Provides biological plausibility, increasing in importance, and KCs could enlighten approaches to testing

3

3

Mechanistic Data: *Challenges*

**IARC Monographs
Volume 100**

- How to search systematically for relevant mechanisms?
- How to bring uniformity across assessments?
- How to analyze the voluminous mechanistic database efficiently?
- How to avoid bias towards favored mechanisms?

4

The Classical Approach to Mechanistic Data has been Hypothesis Driven

Analysis of mechanistic data for hazard identification and risk assessment has typically involved developing a mode of action (MOA) or more recently an Adverse Outcome Pathway (AOP)

5

Key characteristics don't require risk assessor to guess the mechanism

- Mechanistic hypotheses in science are beneficial because if you test it and are wrong then you modify the hypothesis and get closer to the truth

- Mechanistic hypotheses in risk assessment are problematic because if you are wrong you may have made a bad risk decision that cannot easily be changed and may have caused medical or economic harm

6

6

Limitations of MOA/AOP Approach

- Focus on 'favorite' mechanism may introduce bias, especially on committees and public databases
- MOA/AOP may be incomplete or wrong [e.g. DEHP – Rusyn and Corton (2012)]
- How many 'validated' AOPs needed for 100K chemicals producing 100s of adverse outcomes in different ways?
- KCs can help build unbiased MOA/AOPs if they are essential (as in current EPA guidelines)

7

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MOAs can be used to exclude data or make prejudiced conclusions leading to conflicting assessments
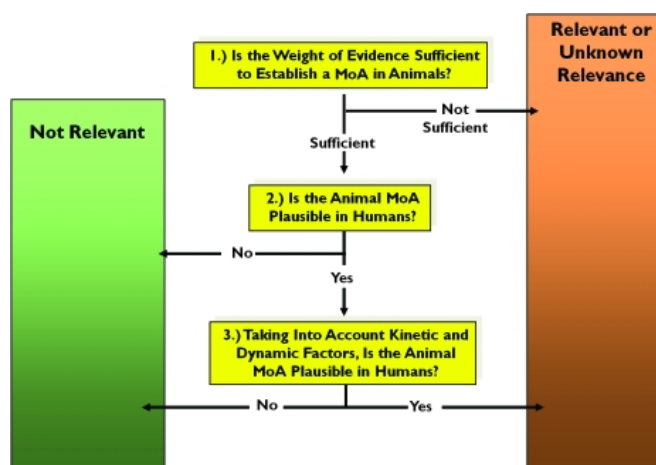
From: Adami, H-O et al. (2011) Toxicology and Epidemiology: Improving the Science with a Framework for Combining Toxicological and Epidemiological Evidence to Establish Causal Inference *Toxicological sci.* 122, 223-34

8

Key Events in a Carcinogenic AOP

None of these common key events are detectable in target tissues

Cancer is at least 200 different disease states
Events need not occur in a serial fashion
MIE is not forced to be a DNA alteration

9

TRAIN SCENE   BUSTER KEATON MOVIE   COTTAGE GROVE
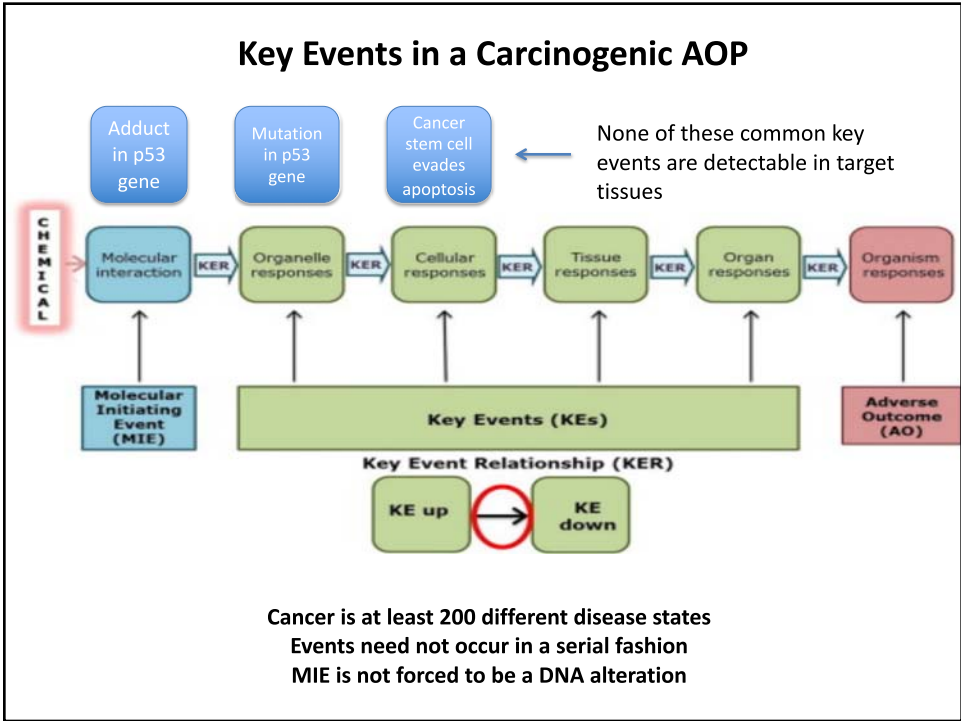
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2017 NAS Report "Using 21st Century Science to Improve Risk-Related Evaluations" –
Comments on the Key Characteristics Approach

- The "approach avoids a narrow focus on specific pathways and hypotheses and provides for a broad, holistic consideration of the mechanistic evidence." (p.144)
- "The committee notes that key characteristics for other hazards, such as cardiovascular and reproductive toxicity, could be developed as a guide for evaluating the relationship between perturbations observed in assays, their potential to pose a hazard, and their contribution to risk." (p.141)

11

Some applications of the KCs

- Searching the literature – Sets of MeSH terms developed – Facilitate systematic review
- Identify data gaps
- Improve predictive toxicology – new assays and computational approaches
- Better understanding of risk from mixtures where chemicals act at different stages of a process

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12

Working Group on KCs of Endocrine Disruptors and Reproductive Toxicants

Berkeley CA, March 7-8, 2018

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Three papers on KCs of reproductive toxicants and endocrine disruptors

1) Proposed Key Characteristics of Male Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment
Xabier Arzuaga, Martyn T. Smith… and Gail S. Prins, *Environ. Health Perspect*., 127 (6), 65001, 2019
2) Proposed Key Characteristics of Female Reproductive Toxicants as an Approach for Organizing and Evaluating Mechanistic Data in Hazard Assessment
Ulrike Luderer, Brenda Eskenazi, Russ Hauser, et al. *Environ. Health Perspect*. 127 (7), 75001, 2019
3) Key Characteristics of Endocrine-Disrupting Chemicals as a Basis for Hazard Identification
Michele A. La Merrill, Laura N. Vandenberg, Martyn T. Smith, William Goodson, et al. *Nature Rev. Endocrinol.* 2020 Jan;16(1):45-57. doi: 10.1038/s41574-019-0273-8. PMID: 31719706

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Current KC Working Groups and Leaders

- Mixtures – Rider and McHale (EHP paper soon)
- Neurotoxicants – Lein and Hartung
- Hepatotoxicants – Rusyn
- Immunotoxicants – Germolec and Lebrec
- Cardiotoxicants – Lind and Smith
- Metabolic disruptors – Blumberg, La Merrill

15

Comparison of Key Characteristics for Different Toxicants

Key Characteristics - Carcinogens	Male Repro	Female Repro	EDC	Neurotox
1. Is electrophilic or metabolically activated	-	-	-	-
2. Is genotoxic	X (5)	X (2)	-	-
3. Alters DNA repair or genomic instability	-	-	-	-
4. Induces epigenetic alterations	X (6)	X (3)	X (5)	X (10)
5. Induces oxidative stress	X (7)	X (5)		X (8)
6. Induces chronic inflammation	X (8)	X (6)	-	X (12)
7. Is immunosuppressive	-	X (6)	-	-
8. Modulates receptor-mediated effects	X (4)	X (1)	X (1, 2, 3, 4)	X (2)
9. Causes immortalization	-	-	-	-
10. Alters cell proliferation, cell death, or nutrient supply	X (1)	X (9)	X (10)	X (1)

There may be key characteristics of bioactive hazardous chemicals
Meeting is being planned on this topic

16

8

Thank you for listening!

https://keycharacteristics.org

Twitter: #KeyChars

Acknowledgements: Financial support from CalEPA OEHHA (Lauren Zeise, Director) and Research Translation Core of NIEHS SRP grant P42ES004705. Thanks to the many scientists who have contributed their time and knowledge to KC development, especially Kathryn Guyton of IARC.

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Thanks to All the KC Working Group Participants
90 people; 43 Institutions; 11 Countries to date

Last Name	First Name	Institution	KC Group(s)
Araujo	Jesus	UCLA	Cardiotox
Arzuaga	Xabier	U.S. EPA (IRIS)	Male repro
Baan	Robert	IARC (retired)	Carcinogens
Barchowsky	Aaron	Uni. Pittsburgh	Cardiotox
Beland	Frederick	FDA (NCTR)	Carcinogens
Belcher	Scott	N. Carolina State Uni.	Cardiotox
Berridge	Brian	NIEHS, NTP	Cardiotox
Beverly	Brandy	NIEHS, NTP	Male repro
Borrel	Alexandre	NIEHS, NTP	Assays & Hallmarks
Bowman	Aaron	Purdue Uni.	Neurotox
Browne	Patience	OECD	EDCs
Bucher	John	NIEHS, NTP	Carcinogens
Caldwell	Jane	US EPA (retired)	Carcinogens
Cao	Zhengyu	China Pharmaceutical Uni.	Neurotox
Cardenas	Andres	UC Berkeley	Assays & Hallmarks
Carson	Monica	UC Riverside	Neurotox
Chen	Tracy	FDA	Cardiotox
Chiamvimonvat	Nipavan	UC Davis	Cardiotox
Chiu	Weihsueh	Texas A&M Uni.	Carcinogens; Assays & Hallmarks; Cardiotox
Christiani	David	Harvard Uni.	Carcinogens
Cogliano	Vincent	OEHHA	Carcinogens; EDCs; Cardiotox
Cooper	Ralph	U.S. EPA (retired)	Female Repro
Corpet	Denis	Université de Toulouse	Carcinogens
DeMarini	David	U.S. EPA	Carcinogens
Elmore	Sarah	OEHHA	Cardiotox
Eskenazi	Brenda	UC Berkeley	Female Repro; Neurotox
Farraj	Aimen	U.S. EPA	Cardiotox
Felsher	Dean	Stanford Uni.	Assays & Hallmarks
Fielden	Mark	Amgen	Assays & Hallmarks
Fritsche	Ellen	IUC, Düsseldorf	Neurotox
Fritz	Jason	U.S. EPA	Carcinogens
Gibbons	Catherine	U.S. EPA	Carcinogens; Male repro; Assays & Hallmarks
Gomes	Aldrin	UC Davis	Cardiotox
Goodson	William	UCSF	EDCs; Assays & Hallmarks
Gore	Andrea	Uni. Texas, Austin	EDCs
Guyton	Kathryn	IARC	Carcinogens; EDCs; Assays & Hallmarks
Harry	Jean	NIEHS	Neurotox
Hartung	Thomas	Johns Hopkins	Neurotox
Hauser	Russ	Harvard	Female Repro; Male Repro
Hecht	Stephen	Uni. Minnesota	Carcinogens
Hotchkiss	Andrew	U.S. EPA, NTP	Male repro
Houck	Keith	U.S. EPA	Assays & Hallmarks
Kavlock	Robert	U.S. EPA	Carcinogens
Kleinstreuer	Nicole	U.S. EPA, NTP	Assays & Hallmarks
Korach	Kenneth	NIEHS	EDCs; Female Repro; Male Repro
Kortenkamp	Andreas	Brunel Uni. London	EDCs
La Merrill	Michele	UC Davis	EDCs; Assays & Hallmarks
Lambert	Paul	Uni. Wisconsin	Carcinogens
Lebrec	Herve	Amgen	Assays & Hallmarks
Lein	Pamela	UC Davis	Neurotox
Lind	Lars	Uni. Uppsala	Cardiotox
Lowe	Leroy	Getting to Know Cancer	Assays & Hallmarks
Luderer	Ulrike	UC Irvine	Female Repro
McHale	Cliona	UC Berkeley	Female Repro; Assays & Hallmarks
Meyer	Kathleen	Sangamo Therapeutics	Cardiotox
Minocherhomji	Sheroy	Amgen, SSF	Assays & Hallmarks
Moran	Pancho	OEHHA	Female Repro
Pagani	Rodrigo	Uni. Illinois, Chicago	Male repro
Patisaul	Heather	N. Carolina State Univ.	EDCs
Portier	Christopher	Maastricht Uni.	Carcinogens
Posnack	Nikki	George Washington Uni.	Cardiotox
Prins	Gail	Uni. Illinois	Male repro
Rider	Cynthia	NIEHS, NTP	Assays & Hallmarks
Rieswijk	Linda	UC Berkeley (now at Maastricht Uni.)	Carcinogens; EDCs; Female Repro; Assays & Hallmarks
Ross	Matthew	Mississippi State Uni.	Carcinogens
Rusyn	Ivan	Texas A&M, College Station	Carcinogens
Sandy	Martha	OEHHA	Male repro; Assays & Hallmarks
Schrader	Steve	NIOSH (ret.)	Male repro
Shafer	Tim	U.S. EPA	Neurotox
Skakkebaek	Niels	Copenhagen Uni.	Male repro
Slikker	Bill	FDA, NCTR	Neurotox
Smith	Martyn	UC Berkeley	Carcinogens; EDCs; Female Repro; Male Repro; Cardiotox; Neurotox; Assays & Hallmarks
Solomon	Gina	UCSF, Public Health Inst.	Female Repro
Sone	Hideko	NIES Japan	EDCs; Assays & Hallmarks
Stewart	Bernard	Uni. New South Wales	Carcinogens
Straif	Kurt	IARC	Carcinogens
Udagawa	Osamu	NIES Japan	Female Repro
van den Berg	Martin	Utrecht Uni. (IRAS)	Carcinogens
Vandenberg	Laura	Uni. Massachusetts, Amherst	EDCs
Vargas	Hugo	Amgen	Cardiotox
Wang	Amy	NIEHS, NTP	Carcinogens; Assays & Hallmarks
Webster	Thomas	Boston Uni.	Assays & Hallmarks
Woodruff	Tracey	UCSF	EDCs
Yang	Xi	FDA	Cardiotox
Yost	Erin	NIEHS, NTP	Male repro
Zeise	Lauren	OEHHA	EDCs; Female Repro; Male Repro; Cardiotox; Neurotox; Assays & Hallmarks
Zhang	Luoping	UC Berkeley	Female Repro; Assays & Hallmarks
Zhou	Changcheng	UC Riverside	Cardiotox
Zlatnik	Marya	UCSF	Female Repro
Zoeller	Thomas	Uni. Massachusetts, Amherst	EDCs

18

9

Evidence synthesis, integration and evaluation: the case of Glyphosate and beyond

Kurt Straif
ISGlobal, Barcelona, Spain and
Boston College, MA, USA

NRDC

UCSF Program on Reproductive Health and the Environment

Milken Institute School of Public Health
THE GEORGE WASHINGTON UNIVERSITY

10 Feb, 2021

1

Divergent evaluations

- **Glyphosate is just one** of more than a 1000 agents that have been evaluated and classified by the IARC Monographs Programme with regards to their potential cancer hazard.

- About one half of all agents have been classified into Group 2B (possibly carcinogenic to humans) or higher, and more than 200 agents have been classified - like glyphosate - into Group 2A (probably carcinogenic to humans) or higher.

- Nevertheless, the systematic review, evidence synthesis, integration and evaluation, of the published scientific literature on glyphosate has probably received **more (and lasting) attention** than the classifications of Radiofrequency EMF (Group 2B), Formaldehyde, Diesel engine exhaust, Processed meat, Oral contraceptives, and Combined estrogen–progestogen menopausal therapy (all Group 1), altogether.

  Perceived magnitude of the (orchestrated) controversy seems to be highly correlated with stakeholder interests (note, this may include different stakeholder perspectives).

- **Perhaps, the overall problem of divergent evaluations is not as big as stated in the introduction to this WS:**
  "good scientists have often evaluated the "same" evidence on hazardous agents very differently"?
  But, few have been as extreme as **glyphosate**, so this may be a **good starting point for lessons learned.**

2

Glyphosate: a case study
IARC evaluation

Cancer in humans (NHL)	**Cancer in animals**	**DNA damage & oxidative stress**
Limited evidence • Studies of real-world exposures (occupational) • *Glyphosate formulations* in different regions at different times	*Sufficient* evidence • Studies of pure *glyphosate* • Rare cancers in valid studies	*Strong* evidence • Few studies of real-world exposures (communities) • Experimental studies of pure *glyphosate* • Experimental studies of *glyphosate formulations*

IARC Evaluation, March 2015

Group 2A *Probably carcinogenic to humans*

3

Divergent evaluations: What has contributed and what not (despite various claims)

Different frameworks for Systematic Review (SR)

• **Hazard identification** (HI) vs **risk assessment** (via the oral route of exposure to dietary residues) – no

Still, need to define "probably carcinogenic to humans" (HI, IARC Preamble)

HI is the first step of risk assessment, and any of the evidence stream-specific evaluations on "sufficient evidence" in exp. animals or "strong evidence" of genotoxicity are incompatible with EU relicensing of G

• Glyphosate vs Glyphosate-based formulations (GBF), particularly tallowamines - no

4

Same evidence base?

- Yes, divergent evaluations were within a relatively small window of time

- But eligibility of studies, eg unpublished cancer bioassays, guideline studies
  Monsanto breaking the embargo: "**cherry picking and junk science**"
  IARC Preamble "…materials may include reports and databases publicly available from government agencies, … The **reliance on published and publicly available studies promotes transparency and protects against citation of premature information**."; re-interpretation of results by stakeholders at ECHA meeting

- C. Portier 2020, Meta-analysis of all cancer bioassays, **Evidence got even stronger**

- Ch. Benbrook 2019, EPA and IARC on genotoxicity: EPA relied mostly **on registrant-commissioned, unpublished regulatory studies, 99% of which were negative**, while IARC relied mostly on peer-reviewed studies of which 70% were positive

5

Subject matter expertise
At level of assessment of individual agents

- Look into various assessments of epidemiological studies, then look for the epidemiological expertise on the panel

FINANCIAL TIMES

November 24, 2015 5:55 pm

A false alarm on red meat and cancer
Gordon Guyatt

Share ⌄   Author alerts ⌄   Print   Clip

Two large trials have tested for evidence and the WHO ignored both of them, writes Gordon Guyatt

"So the WHO leaned heavily on the third source: epidemiological data. … Unless relative risks are greater than five, epidemiological studies typically provide only low-quality evidence."

- BfR: must use the statistical tests as described in Methods of a study – no,

IARC Preamble provides clear guidance on statistical analysis of cancer bioassays, eg, appropriate use of historical controls in rare cancers

6

Subject matter expertise

At level of development of frameworks for SR

Annals of Internal Medicine   IDEAS AND OPINIONS

GRADE Methods for Guideline Development: Time to Evolve?

Susan L. Norris, MD, MPH, MSc, and Lisa Bero, PhD

- "not currently applicable to many questions that guideline developers face, including those about assessing risk and causality, establishing risk thresholds, or assessing animal studies."
- First EFSA guidelines on the interpretation of epidemiological studies (now revised and improved, with expert epidemiologists T. Fletcher, N. Pearce)
- ROBINS-E, originally developed without expertise from environmental epidemiology experts (Steenland et al, 2020)
- …

7

Conflict of Interests

At level of development of frameworks for SR

- COSTER authors, Declaration of Competing Interest: "objective of the project being to establish, across a wide range of stakeholders… no apparent competing financial interests"

  While COSTER guidelines are highly prescriptive, surprisingly a strict conflict of interest management was not considered necessary for the conduct of SR
- ROB tool, **Definitely Low-risk (Ideal Study)** "Authors state that there are no conflicts of interests OR state that the funders did not have a say in the methods, analysis and reporting of results"

At level of assessment of individual agents

- **WHO/FAO JMPR**, letter by Dr Sass (NRDC) about hidden CoI regarding glyphosate re-evaluation vs **IARC** "Invited Specialist"
- **BfR** (German Federal Institute for Risk Assessment) report on glyphosate for EFSA's assessment for re-licensing of glyphosate ghost-written by Glyphosate Task Force
- **EFSA** asked experts for approval to disclose CoI, but experts declined
- New dimension …

8

Hollingsworth

Ranjit S. Dhindsa
dir 202 898 5806

August 18, 2016

PRIVILEGED AND CONFIDENTIAL

VIA ELECTRONIC MAIL

Dr. Warren G. Foster
McMaster University
Department of Obstetrics & Gynecology
1280 Main Street West, HSC-3N52D
Hamilton, Ontario, Canada L8S 4K1

Re: Monsanto Roundup® Litigation

Dear Dr. Foster:

You also agree to maintain the fact that you have been retained by HLLP as strictly confidential and privileged

information exchanged between HLLP and you (whether orally or in writing) as strictly confidential and privileged, unless we inform you, at some time in the future, that certain information needs to be disclosed in the Litigation. You also agree to maintain the fact that you have been retained by HLLP as strictly confidential and privileged, unless we inform you, at

9

Risk of bias (ROB)

General issues in the application of GRADE to environmental health
- Initial level of certainty in absence of Randomized Control Trials (up/downgrading)
- Risk of bias
- Assessment of inconsistencies and heterogeneity
- Assessment of Publication bias
- Lack of evaluation of consistency across study designs and populations
- Algorithms in the ROB assessment and scoring

10

Risk of bias (ROB)

- ROB assessments typically focus on whether specific biases are present, but do not usually assess the direction, magnitude, or overall importance
- Information bias unlikely to explain positive findings of studies with non-differential exposure misclassification
- ROB tools typically evaluate bias in individual studies and consider individual studies out of context.
- Assessments often used to exclude "low-quality" studies from ES.
- ROB tools rarely assessed for construct validity
  - Navigation Guide, Comparison of different ROB tools:
  Tool with the highest inter-observer kappa, driven by one domain (reporting of study power): many studies being consistently rated as low;
  - S Norris commented on "low interrater reliability when assessing complex bodies of evidence consisting of different study designs".
  Yet, high inter-rater reliability is necessary, but not sufficient
- US NAS recommended "not too prescriptive" tools to ensure the expert judgement is comprehensive and transparent

11

Funding of research and data accessibility

- Little funding into causes of cancer vs genetics and personalized medicine
- Glyphosate THE most widely used herbicides, but almost no published exposure data at time of IARC Monographs meeting;
- Stakeholder access to US NCI data for re-analysis (e.g., formaldehyde, diesel engine exhaust) vs no access for academia to industry-funded studies and decreasing access to study health risks among worker populations (e.g., almost no studies among workers in pesticides manufacturing)

12

Publication of research

- Blocking publication of NCI/NIOSH studies on carcinogenicity of diesel engine exhaust (DEE)
- Withdrawal of accepted studies after take-over of journal by industry (Séralini, glyphosate; Egilman, IJOEH, asbestos)
- Industry-funded studies not available for independent scrutiny
- Ghost-written articles and commentaries by industry
- Weakness of Conflict of Interest procedures (Tarone, glyphosate; Gamble, DEE) and Committee on Publication Ethics (COPE)

Industry group "threatens" journals to delay publications

Several scientific journals, including *The Lancet* titles, have received letters from the industry-funded Mining | *Annals of Occupational Hygiene* (which also received MARG's letter) and the *Journal of the National Cancer Institute,* | for publication, except through normal peer review", said Vincent Cogliano, a former IARC Monographs Programme

13

Perspectives

- Ultimately, the question for policy makers and society is: how much evidence is enough to take action?
- The answer may vary by type of exposure and options for action
- Strong evidence of carcinogenicity in animals OR strong evidence of genotoxicity would normally be sufficient to stop re-licensing a pesticide according to pesticide regulations
- In the workplace, strong evidence of carcinogenicity in animals typically triggers the full hierarchy of industrial hygiene controls, prominently including strict occupational exposure limits.

14

Conclusions

- Evidence synthesis and causal inference should include the use of classical considerations for judging causality, triangulation, and integration of epidemiological, bioassay and mechanistic data.

- Observational studies should be judged on their own merits, within the context of an optimal design for the exposure-outcome of interest, and in the broader evidence synthesis context.

- ROB assessments should try to identify and quantify important biases, their direction, and their impacts on effect estimates.

- Risk of bias assessments should be done with knowledge of the specific context, rather than primarily ruling out individual studies.

- Aspects of study informativeness - the ability of a study to show a true association, if there is one - need to be considered

- Evidence synthesis requires expert groups with sufficient interdisciplinary subject matter expertise and

- Strong procedures for conflict of interest management, public engagement and stakeholder involvement

15

Question to the Breakout group

What are the key elements of systematic evaluations of harmful agents and what are the barriers to their more widespread use by hazard and risk assessment committees?

16

Governing complex risks when evidence is limited
– from SOER2020 to the EU chemicals strategy for sustainability

Xenia Trier, Ph.D.
Expert on chemicals, environment and health
European Environment Agency

Workshop on Conducting Evaluations of Evidence that are Transparent, Timely and Lead to Health-Protective Actions
February 10th 2021

Upstream prevention of risk

Strengthened legislation

Safe and Sustainable by design

Non-toxic material cycles

Grouping of chemicals

Vulnerable groups

Non essential uses

PFAS and Mixtures

Impacts of chemicals on EH&HH

European Environment Agency
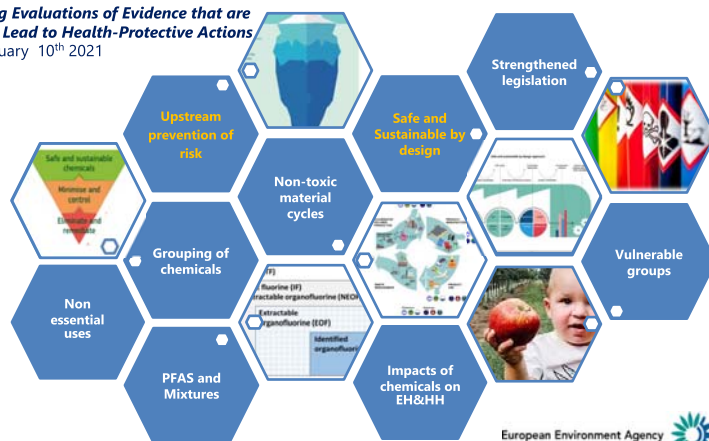
1

Who cares about chemical pollution…?

Europe is the second largest producer with **16.9%** of global sales

EU chemicals industry employs **1.2 million** people

59% of chemicals supplied to other sectors, such as health, constructions, automotive, electronics, textiles

84% Europeans are worried about the impact of chemicals present in everyday products on their health

90% Europeans are worried about the impact of chemicals on the environment

European Environment Agency

2

State and Outlook on the Environment (SOER2020) - Systemic view on chemical pollution

- Human activities lead to point and diffuse chemical pollution
- Pollution moves across boundaries
- Emissions occur along lifecycles
- Total burden of mixtures of chemicals impacts people and the environment

=> what is the status and outlook on chemical pollution and impacts?
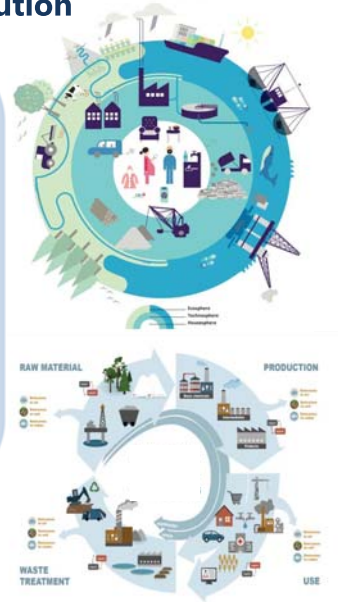
Read our Report Europe's environment – State and Outlook
https://www.eea.europa.eu/publications/soer-2020/chapter-10_soer2020-chemical-pollution/

3

SOER2020 – reduction in emissions of POPs and substances of very high concern(SVHCs)

Chart – Change in hexachlorobenzene emissions
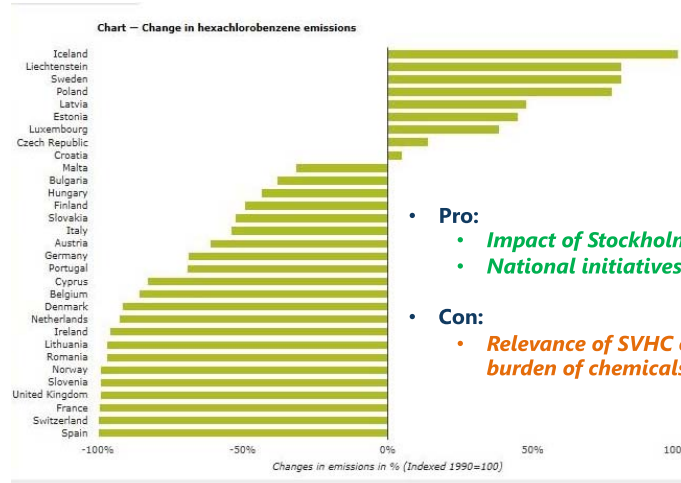
- Pro:
  - *Impact of Stockholm convention*
  - *National initiatives*
- Con:
  - *Relevance of SVHC emissions cf total burden of chemicals?*

Changes in emissions in % (Indexed 1990=100)

European Environment Agency

4

How to interpret reduction in SVHC emissions?

H. Wöhrnschimmel et al. / Environmental Pollution 217 (2016) 149–158

- **Mostly reductions in measured legacy POPs, but also constant or increases in others**
  - Differences between remote and urban areas (time-lags)
  - Explanation of reductions:
    Likely impact of both SC, RoHS and national initiatives

- **Impacts of POPs continue to be high and add to total burden of chemicals**
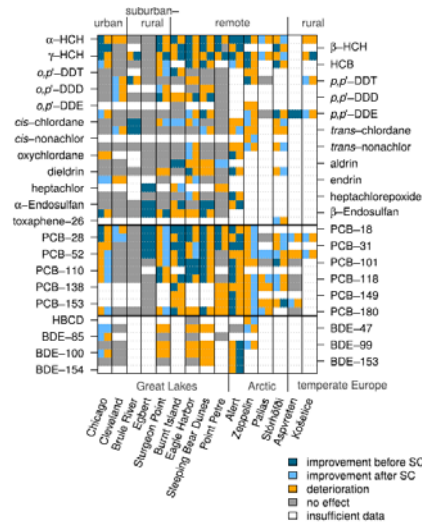
Fig. 5. Summary of structural changes in POP time series. Two color fields within a grid cell indicate two subsequent trend changes in one time series (SC = Stockholm Convention).

5

SOER2020: Success or regrettable substitution?

- Reduction in the use of Ozone Depleting Substances (ODS) – success! ☺ !
- Increased use of green house F-gasses => regrettable substitution - ☹
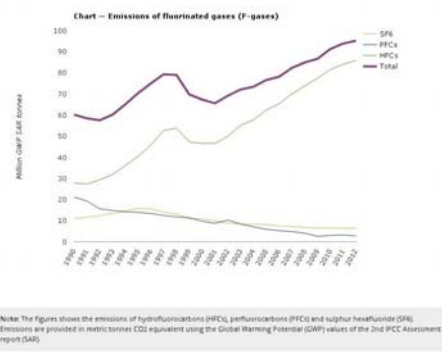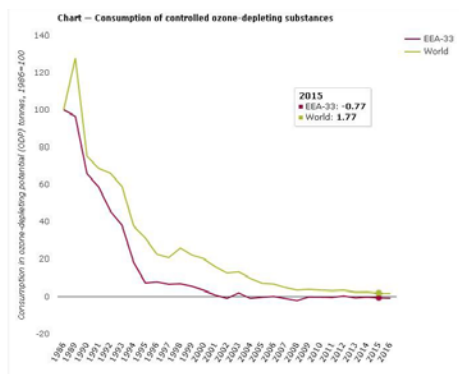
https://www.eea.europa.eu/data-and-maps/indicators/production-and-consumption-of-ozone-2/assessment-3
https://www.eea.europa.eu/data-and-maps/indicators/emissions-and-consumption-of-fluorinated/assessment-2

6

Impact on ecosystems – which endpoint?

Example of acute vs. chronic toxicity of single chemicals in European rivers/lakes
- Used most senstive endpoint on aquatic organisms, mixtures not included
- *Which protection goals?*
- *Which toxicological endpoints?*
- *Which chemicals?*

Acute risk | Chronic risk

Chemical risk estimates for European river basins (%)

< 10 10-25 25-50 50-75 75-100 < 6 sites No data

(Maps have been adapted from Malaj et al. 2014)
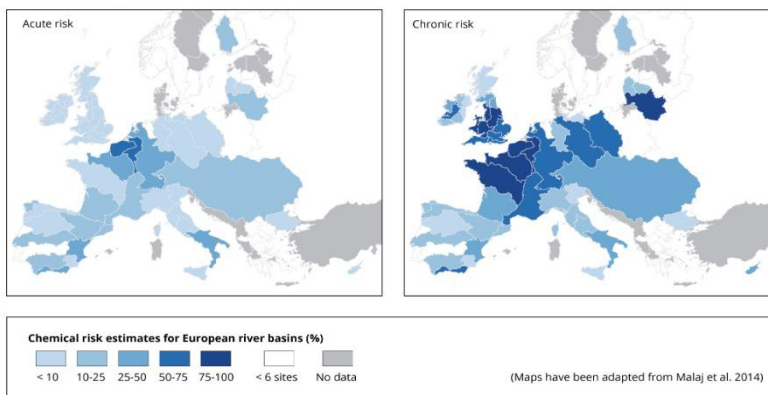
7

Risk assessment cannot keep up with >100,000 chemicals

~ 100 000 chemicals on the market

RISKS

HAZARDS   EXPOSURES

~ 500 chemicals extensively characterised for their hazards and exposures

~ 10 000 chemicals fairly well characterised for a subset of their hazards and exposures

~ 22 600 chemicals with a use over 1 tonne

~ 4 700 with a ... 100 tonne prioriti... hazard char... and evalu...

Diversity and volumes of chemicals increase

New approaches for risk governance are needed
- Coherence across policy domains
- Life-cycle approach
- **Address mixtures, in RA and implementation**
- Transition to 'safe and sustainable by design' products

iropean Environment Agency

8

Chemical pollution summary assessment

Thematic summary assessment

Theme	Past trends and outlook		Prospects of meeting policy objectives/targets
	Past trends (10-15 years)	Outlook to 2030	2020
Emissions of chemicals	Trends show a mixed picture	Deteriorating developments dominate	☒ Largely not on track
Chemical pollution and impacts on ecosystems	Trends show a mixed picture	Deteriorating developments dominate	☒ Largely not on track
Chemical pollution and risks to human health and well-being	Trends show a mixed picture	Deteriorating developments dominate	☒ Largely not on track

Note: For the methodology of the summary assessment table, see the introduction to Part 2. The justification for the colour coding is explained in Section 10.3, Key trends and outlooks (Tables 10.2, 10.3 and 10.4).

European Environment Agency

9

What is the Chemicals Strategy for Sustainability (CSS) towards a toxic-free environment - aims

Safe and sustainable chemicals
Minimise and control
Eliminate and remediate

1. Chemicals are produced/used in a way that maximises their benefits to society while avoiding harm to planet & people

2. Production and use of *safe and sustainable chemicals* becomes the EU market norm and a global standard

Credit: Elena Montani, DG ENV

Documents:
- **The CSS:** https://ec.europa.eu/environment/strategy/chemicals-strategy_en
- **Annex to CSS with actions and timelines**
- **Mixtures staff working document (SWD)**
- **PFAS staff working document (SWD)**

European Environment Agency

10

11
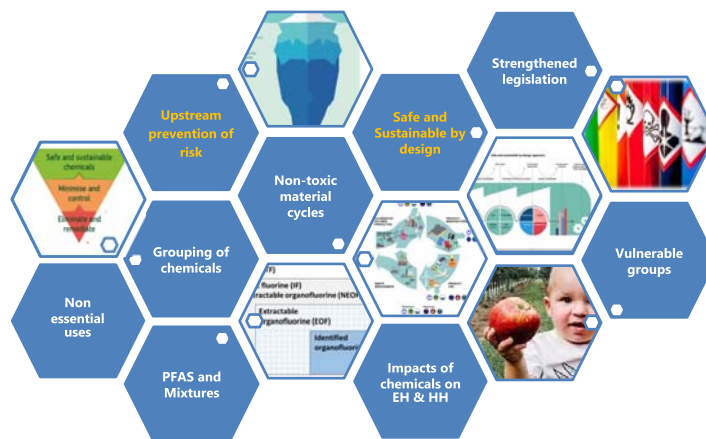
Figure 2: Detailed visual representation of the IRGC Risk Governance Framework.

IRGC. (2017). An introduction to the IRGC Risk Governance Framework

12

National Institute for Public Health and the Environment
Ministry of Health, Welfare and Sport

Conducting Evaluations of Evidence that are Transparent, Timely and Lead to Health-Protective Actions. Feb 8-11, 2021

Core beliefs, weights of evidence and handling uncertainties in risk assessment – PFOA case study

February 9, 2021

Theo Vermeire, RIVM, Bilthoven

1

Risk assessment paradigm   hard science?

HAZARD IDENTIFICATION
defines which chemicals, biological or physical agents are potentially harmful to human health or the environment. It can be based on the results of in vivo tests, in vitro tests, in silico methods, epidemiological studies, clinical studies, case reports and data from post-marketing surveillance.

DOSE-RESPONSE ASSESSMENT
describes the relationship between the extent of an adverse effect in an organism and the different concentrations or doses of a chemical.

EXPOSURE ASSESSMENT
defines the human exposure levels. It determines or estimates how, how much and how often the population is exposed to a substance. It also defines the source and the route of intake.

RISK CHARACTERISATION
is the combination of information on hazard, exposure, and dose response to provide an estimate of the probability that identified specific adverse effects will occur in exposed people.

2

2

Some lessons from psychology - risk perception & communication

- Risk is more than a number coming from analytical risk assessment

- Many people struggle with interpreting results, probabilities

- Risk is often perceived as a social construct and a feeling

- Facts are not sufficient to describe acceptable risk

- Conflicting views from experts increases uncertainty

- Scientist (often unwittingly) play a role in social amplification/ attenuation of risks

3

3

Working on environmental health issues from different perspectives

4

4

2
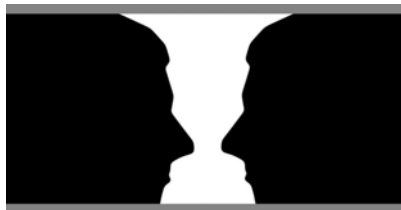
Scientific reasoning in controversies

- While science is often seen as '**value free**', universal and independent, quite often scientific controversies about environmental health issues are convoluted by (implicit and hidden) **normative value judgements** from experts and by their **professional paradigms**.

- From argumentation analysis of controversial scientific positions on **Endocrine Disruptive Compounds**, we have identified the structure of argumentation and observed that the differences in the main standpoints differed in the nature of the disagreement; some were disagreement on **interpretation of science** (interpretative ambiguity), while others mainly differed in **normative valuation** (normative ambiguity, value-based positions, e.g. ('early action' vs. 'necessity of robust scientific insights before action'). The latter cannot be resolved under the adage 'more research is needed'.

Clahsen, SCS, van Kamp, I, Hakkert, BC, Vermeire, TG, Piersma, AH, Lebret, E (2018) Why do countries regulate environmental health risks differently? A theoretical perspective. Risk Analysis 39: 439-461, DOI: 10.1111/risa.13165.
Clahsen, SCS, van Klaveren, HS, Vermeire, TG, van Kamp, I, Garssen, B, Piersma AH, Lebret, E (2019): Understanding conflicting views of endocrine disruptor experts: a pilot study using argumentation analysis, Journal of Risk Research 23:1, 62-80, DOI: 10.1080/13669877.2018.1517378
Clahsen, SCS, Moss, L, van Kamp, I, Vermeire, TG, Garssen, BJ, Piersma, AH, Lebret, E (2020) Analysis of different preferences for the EU's regulatory options for endocrine disruptor identification criteria using argumentation theory. Science of the Total Environment 740.2020.140076, DOI.org/10.1016/j.scitotenv.2020.140076

5

5

Concepts, frameworks and theories encountered

- Risk assessment/Risk management Paradigm (RAP)
- Psychometric Risk Paradigm (PRP)
- Cultural theory - Myth of Nature (CTR)
- Advocacy Coalition Framework (ACF)
- Social Amplification of Risk Framework (SARF)
- International Risk Governance Framework
- Hofstede's model of national cultures (HMNC)
- Regulatory frameworks (food safety, chemicals, radiation, cosmetics,….)
- Legal frameworks
- Advisory Roles of Experts in Risk Management Processes (ARERMP)
- What have you…..

6

6

Interaction between coalitions through the exchange of argumentation

TIMELINE – TYPICAL EXAMPLE OF POLEMIC BETWEEN COALITIONS 'A' AND 'B'

Initiating event

Arg. and framing coalition B

Arg. and framing coalition B

Moment of policy intervention

Argumentation and framing [SARF] used by advocacy coalition A [ACF]

Arg. and framing coalition A

Arg. and framing coalition A

Argumentation and underlying beliefs of a coalition

'Discourse' level

Argumentation referring to scientific knowledge | Argumentation referring to normative positions

'Cognitive' level; surface - issue specific [ACF]

Professional context

Personal context

Professional knowledge and beliefs used to interpret the risk issue | Personal knowledge and beliefs used to interpret and evaluate the risk issue

Determinants of expert roles [ARERMP]: Professional paradigm (e.g. [RAP]), Institutional affiliation, Etc.

Social norms and community culture [CTR]

'Cognitive' level; fundamental – broad [ACF]

Specific examples of specific deep core beliefs [ACF]:

Weiss' typology [ARERMP]: *Environmental absolutist - Cautious env. – Env. centrist – Tech. optimist - Scientific abs.*

Myths of Nature [CTR]: *Nature benign - Nature emphemeral - Nature robust, within limits - Nature capricious*

Cultural worldviews [CTR]: *Hierarchist – Egalitarian – Fatalist - Individualist*

Characteristics of one's national culture [HMNC]

7

Views on experimental toxicology and epidemiology

8

8

4

Share 'allergies' and 'deal breakers'

Tox → Epi	Epi → Tox
• Poor exposure info • Term 'Risk factors' for non-causal associations • Use of Relative Risk instead of Absolute Risk • ΣARF > 100% • Inventing data through imputation	• Unrealistic exposure regimes • Experimental conditions • Mono-causal reasoning • Use of health protection based protocols to assess risk in human populations

9

9

		Field of expertise	
		Toxicology	**Epidemiology**
Starting point category	Causality	The experimental study design allows the determination of the dose-response relationship of a chemical compound.	The health outcome measured in the population emerges from a combination of component causes (including the chemical exposure) working together, none of which is in itself a 'sufficient and necessary' cause (Rothman et al., 2012).
		An observed dose-response relationship in protocolled animal studies is generally inferred with certainty as a causal relationship between exposure and effect.	There is extensive discourse on the inference of causality in epidemiological observations (apart from randomised clinical trials). Inferences about causality often take into account Bradford Hill's viewpoints (Hill, 1965).
	Methodology	Adverse effects and the dose-response curve seen in animals are relevant for humans unless scientific evidence indicates otherwise.	Animal studies cannot sufficiently reflect the complexities and interactions with other component causes necessary to induce health effects in the human population.

10

Methodology

- Four risk assessments and HBGVs derivations of PFOA have been analyzed
  - RIVM 2016 (Netherlands)
  - UBA 2018 (Germany)
  - EFSA 2018 (European Union)
  - US-EPA 2016 (United States of America)

- Pragma-Dialectic-Argumentation-Theory (PDAT) applied to
  - Selection of health endpoints of concern
  - Inference of causality between exposure and health effects
  - Choice of animal or human data for derivation of HBGV

van Eemeren, FH, Garssen, B, Krabbe, E, Henkemans, AFS, Verheij, B, and Wagemans, JHM. 2014. *Handbook of Argumentation Theory*. Dordrecht: Springer.

12

Scientific reasoning in controversies

- *Essential argumentation is missing* in all analysed risk assessment reports that would provide insight into the underlying motives for the preference to use epidemiological or toxicological data:
  - ➢ No argumentation
  - ➢ Weak points in data from one research field (either toxicology or epidemiology) criticism of the other field of profession automatically leads to adopting the data of the other field.
  - ➢ Limitations of both fields are highlighted, yet it is not clarified what the final data choice was based on.
  - ➢ Consistency most common reason (not) to use certain studies
- Argumentation on causality is mainly symptomatic (= an argument refers to a sign or typical feature that is relevant for the standpoint, thereby supporting it; starting points and beliefs not expressed).

Jongeneel WP, van Klaveren H, Bogers RP, Dévilée J, Piersma A, Vermeire T, Lebret, E, Rijs KR (2021) Argumentation analysis of risk assessments: the case of PFOA. To be published.
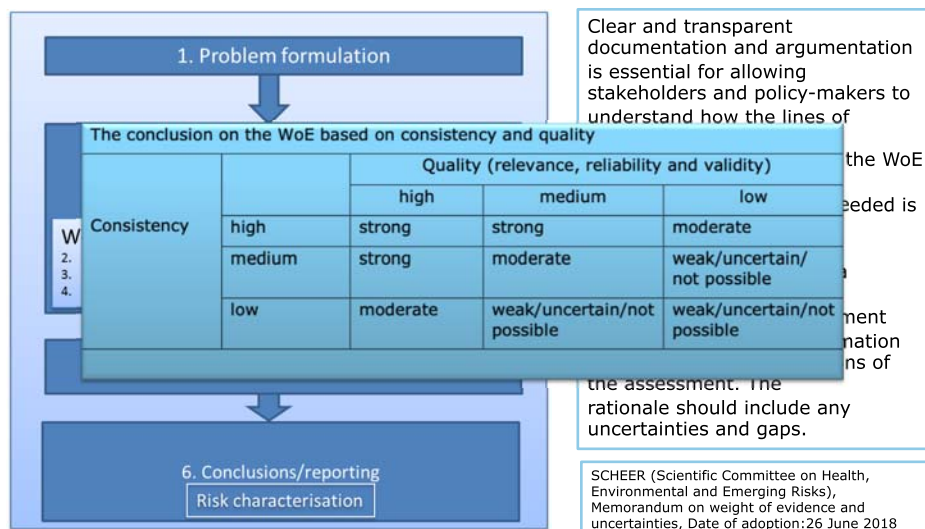
13

Conclusion and discussion

- Differences in *starting points* can lead to discrepancies between the derived HBGVs.

- Most of the communication occurs at the level of conclusions
  > actual interpretation of data,
  >>methodology and the underlying starting points.

- Essential to identify differences in starting points and beliefs between epidemiologists and toxicologists

- Selection of a Point of Departure (PoD) for the derivation of a HBGV is case by case

- A large part of the argumentation needs to be revealed and made explicit.

14

Weight-of-Evidence

1. Problem formulation

The conclusion on the WoE based on consistency and quality

Consistency	Quality (relevance, reliability and validity)		
	high	medium	low
high	strong	strong	moderate
medium	strong	moderate	weak/uncertain/ not possible
low	moderate	weak/uncertain/not possible	weak/uncertain/not possible

6. Conclusions/reporting
Risk characterisation

Clear and transparent documentation and argumentation is essential for allowing stakeholders and policy-makers to understand how the lines of ... the WoE ... eeded is ... ment ... nation ... ns of the assessment. The rationale should include any uncertainties and gaps.

SCHEER (Scientific Committee on Health, Environmental and Emerging Risks), Memorandum on weight of evidence and uncertainties, Date of adoption:26 June 2018

15

https://ec.europa.eu/health/scientific_committees/scheer_en

15

7

Way ahead

➢ Develop broader understanding about other disciplines' perspectives, paradigms and reasoning

➢ Share your 'allergies' and 'deal breakers'; (critically) accept other professional's perspectives

➢ Take all available evidence (regardless of subject area) as starting point for knowledge synthesis and causal inference

➢ To avoid interpretative ambiguity:
  ❖ All lines of evidence should be weighed individually and taken all together for a final conclusion on causal relations.
  ❖ Thoroughly compare quality/weight of evidence approaches. WoE criteria (including clear and transparent documentation and argumentation) still need to be firmly established in risk assessment.

➢ Clear argumentation in causal reasoning will help to disentangle interpretation of science and normative valuation (value-based positions) and to improve the risk communication.

➢ While trust is important, 'getting the facts right' is prerequisite for long-term trust

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16

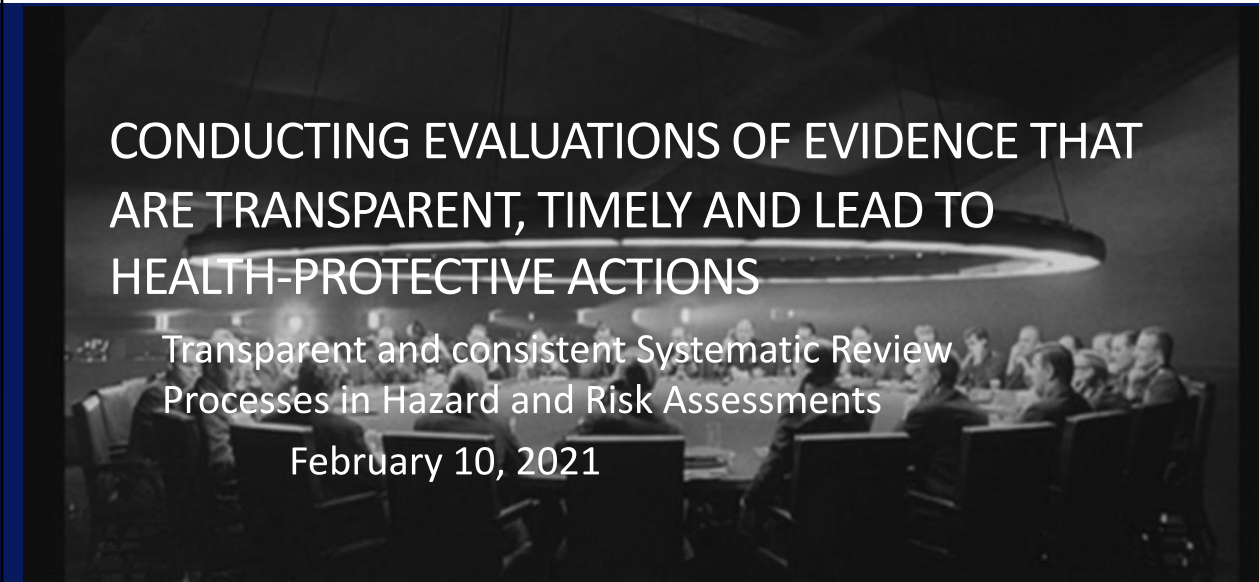## Acknowledgements

Rik Bogers (RIVM)
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Aldert Piersma (RIVM, Un. Utrecht)
Kelly Rijs (RIVM)
SCHEER
(www.https://ec.europa.eu/health/scientific_committees/scheer_en)

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8

CONDUCTING EVALUATIONS OF EVIDENCE THAT ARE TRANSPARENT, TIMELY AND LEAD TO HEALTH-PROTECTIVE ACTIONS

Transparent and consistent Systematic Review Processes in Hazard and Risk Assessments

February 10, 2021

UCSF Program on Reproductive Health and the Environment

1

Nothing to Disclose

2

Navigation Guide: A rulebook for "moving from knowing to doing"
Systematic Review Method for consistently and transparently evaluating evidence that reduces bias

2009

3

Tested, endorsed by NAS, used by WHO/ILO

4

Slide 5

Incorporates considerations from our discussions
- Transparency
- Predefined approach
- Consistency in approach
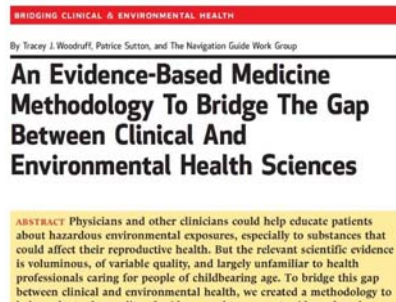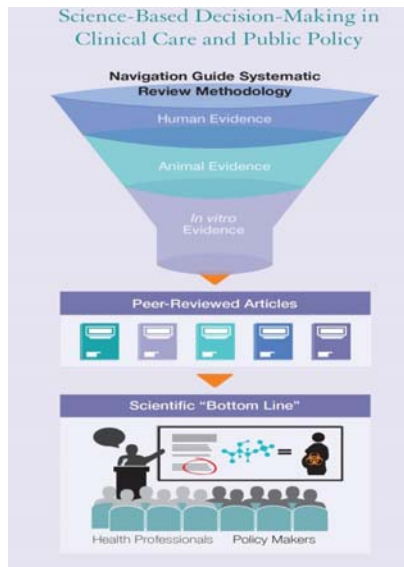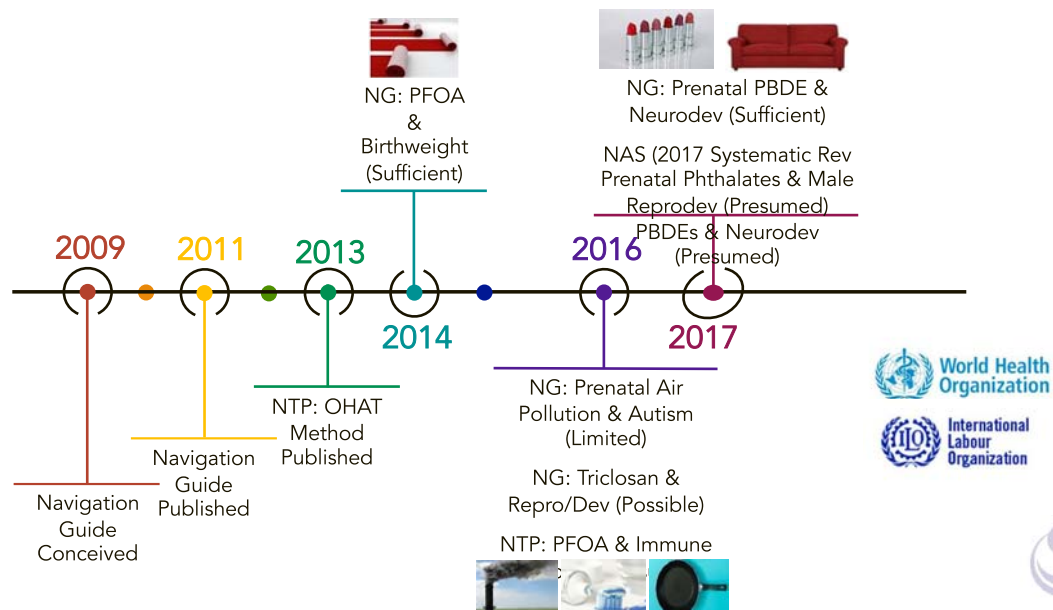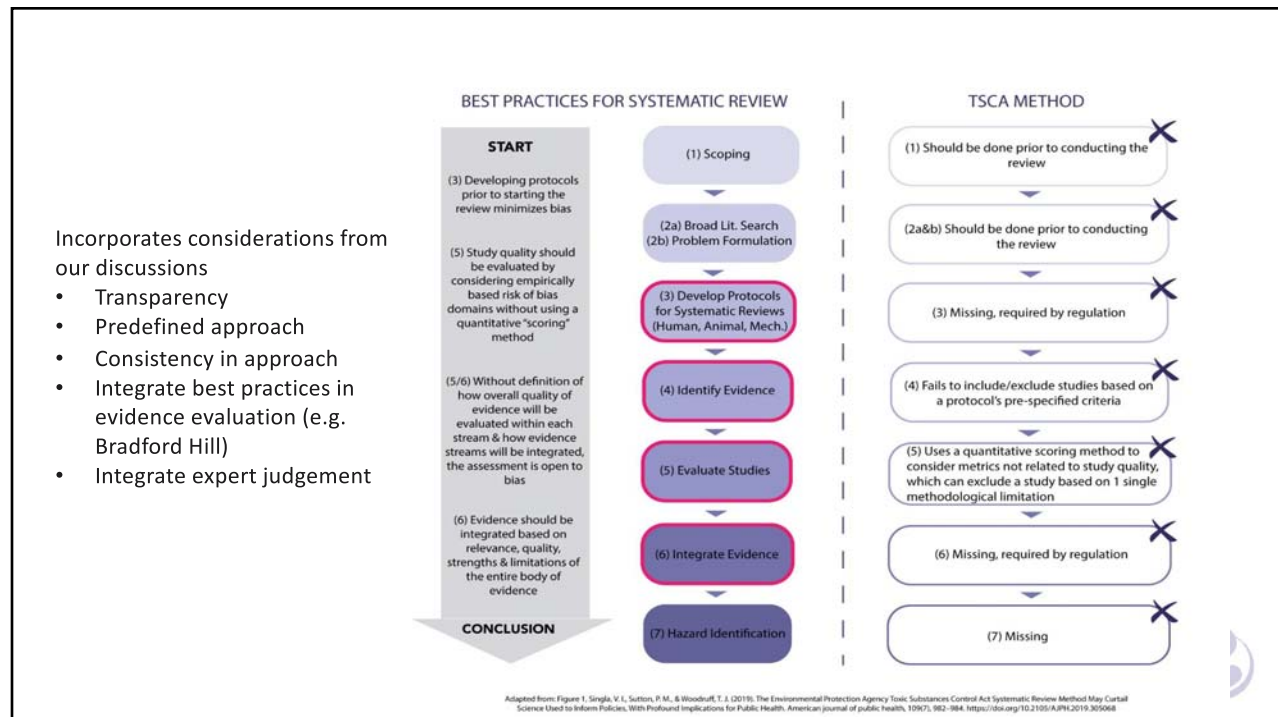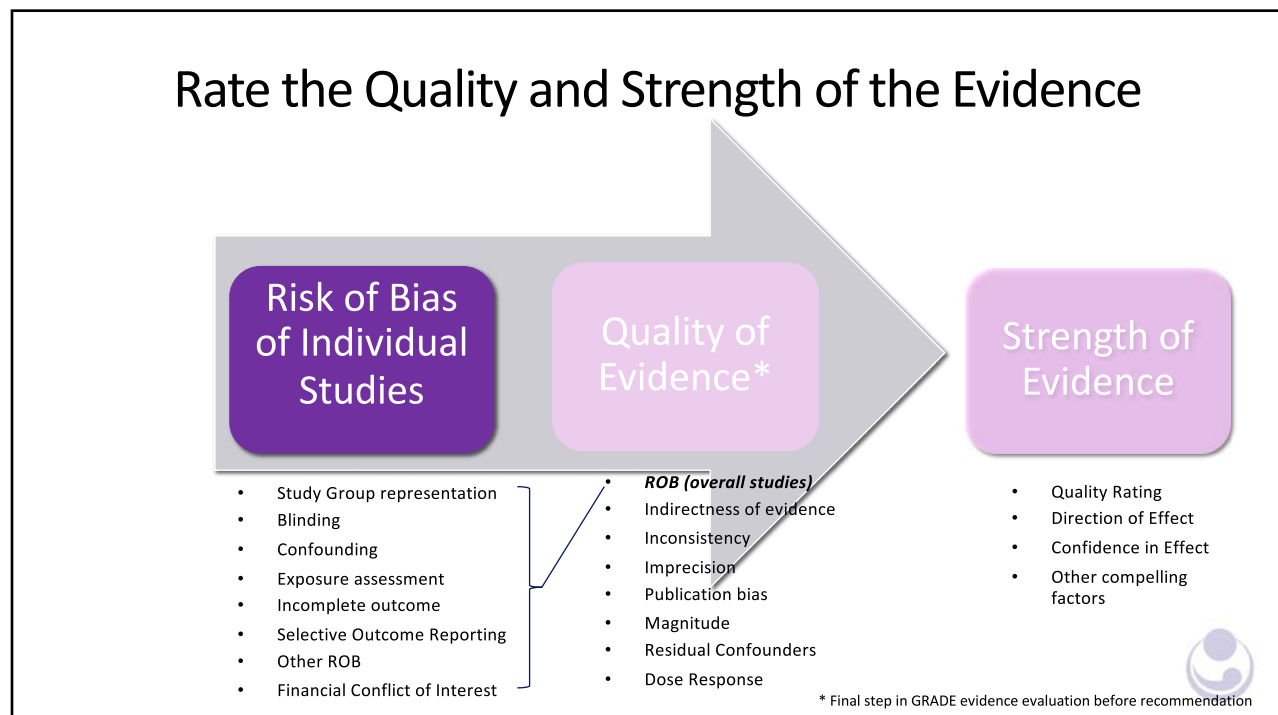- Integrate best practices in evidence evaluation (e.g. Bradford Hill)
- Integrate expert judgement

BEST PRACTICES FOR SYSTEMATIC REVIEW

START

(3) Developing protocols prior to starting the review minimizes bias

(5) Study quality should be evaluated by considering empirically based risk of bias domains without using a quantitative "scoring" method

(5/6) Without definition of how overall quality of evidence will be evaluated within each stream & how evidence streams will be integrated, the assessment is open to bias

(6) Evidence should be integrated based on relevance, quality, strengths & limitations of the entire body of evidence

CONCLUSION

(1) Scoping
(2a) Broad Lit. Search (2b) Problem Formulation
(3) Develop Protocols for Systematic Reviews (Human, Animal, Mech.)
(4) Identify Evidence
(5) Evaluate Studies
(6) Integrate Evidence
(7) Hazard Identification

TSCA METHOD

(1) Should be done prior to conducting the review
(2a&b) Should be done prior to conducting the review
(3) Missing, required by regulation
(4) Fails to include/exclude studies based on a protocol's pre-specified criteria
(5) Uses a quantitative scoring method to consider metrics not related to study quality, which can exclude a study based on 1 single methodological limitation
(6) Missing, required by regulation
(7) Missing

Adapted from Figure 1, Singla, V. I., Sutton, P. M., & Woodruff, T. J. (2019). The Environmental Protection Agency Toxic Substances Control Act Systematic Review Method May Curtail Science Used to Inform Policies, With Profound Implications for Public Health. American journal of public health, 109(7), 982–984. https://doi.org/10.2105/AJPH.2019.305068

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Slide 6

Rate the Quality and Strength of the Evidence

Risk of Bias of Individual Studies

Quality of Evidence*

Strength of Evidence

- Study Group representation
- Blinding
- Confounding
- Exposure assessment
- Incomplete outcome
- Selective Outcome Reporting
- Other ROB
- Financial Conflict of Interest

- *ROB (overall studies)*
- Indirectness of evidence
- Inconsistency
- Imprecision
- Publication bias
- Magnitude
- Residual Confounders
- Dose Response

- Quality Rating
- Direction of Effect
- Confidence in Effect
- Other compelling factors

* Final step in GRADE evidence evaluation before recommendation

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3

Risk of Bias - Characteristics of a study that can introduce systematic errors in magnitude or *direction* of results (measure of internal validity)

1. Study group representation
   Study groups at risk of not representing source population that might introduce selection bias?

2. Blinding
   Were study personnel, outcome and exposure assessor

3. Exposure assessment
   Was there any risk of exposure misclassification?

4. Outcome Assessment Methods

5. Confounding
   Were important confounders considered or adjusted for?

6. Incomplete outcome data
   Were outcomes reported selectively?

7. Selective outcome reporting
   Any reporting discrepancies from outcomes specified in m   ?

8. Financial conflicts of interest
   Was study supported by entity with financial interest?

9. Other potential threats to validity
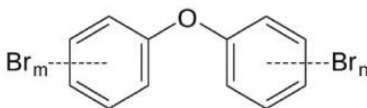   *Any other problems that could bias?*

Modified Cochrane Collaboration Human "Risk of Bias" Tool

Domains used in Nav Guide similar to National Toxicology Program OHAT method

7

PBDE Flame Retardants Used in Wide variety of products Since 1970's

Textiles

People

Foam inside furniture, baby products

Electronics cases

8

Expert narrative review of Prenatal PBDE exposure and Neurodevelopment concludes ???????

CONCLUSION:
"Although **most of the reviewed studies suggest an association** between PBDE exposure and neurodevelopmental outcomes in children"

"the **strength of the reported association varies** widely both between and within studies depending on the age at assessment and the test used to measure the outcome considered."

"There are several **concerns regarding both the internal and external validity** of these studies that, while not entirely undermining the observed associations"

"suggest the need for further exploration before definitive conclusions may be reached."

Gibson, et al 2018

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Systematic Review using Navigation Guide found sufficient evidence PBDE linked to IQ (2017)

ehp Environmental Health Perspectives

Environ Health Perspect. 2017 Aug; 125(8): 086001.   PMCID: PMC5783855
Published online 2017 Aug 3. doi: 10.1289/EHP1632   PMID: 28799918
Review

Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis

Juleen Lam, Bruce P. Lanphear, David Bellinger, Daniel A. Axelrad, Jennifer McPartland, Patrice Sutton, Lisette Davidson, Natalyn Daniels, Saunak Sen, and Tracey J. Woodruff

Herbstman et.al. 2010	−2.69 [−9.28, 3.89]
Eskenazi et.al. 2013	−3.80 [−8.30, 0.70]
Chen et.al. 2014	−4.17 [−8.90, 0.56]
Gascon et.al. 2011	−3.10 [−17.63, 11.43]
RE Model	−3.70 [−6.56, −0.83]

Observed Outcome

Reduced IQ

APPLICATION OF SYSTEMATIC REVIEW METHODS IN AN OVERALL STRATEGY FOR EVALUATING LOW-DOSE TOXICITY FROM ENDOCRINE ACTIVE CHEMICALS

NATIONAL ACADEMY OF SCIENCES

Used our systematic review and also concluded PBDES 'presumed' hazard to human intelligence

10

Methods Matter
Case study - does Risk of Bias Tool influence Systematic Review findings?

NTP OHAT

- Domain based tool, No overall study quality rating
- 7 domains:
  - Participant selection
  - Detection – exposure
  - Detection - outcome
  - Confounding
  - Attrition/exclusion
  - Selective reporting
  - Other
- Answer ROB options: "Definitely low", "Probably low", "Probably high", "Definitely high"

USEPA TSCA Method

- Domain-based tool uses a "quality-based" scoring system
- 22 metrics grouped into 6 domains:
  - Study population
  - Exposure characterization
  - Outcome assessment
  - Potential confounding/variable control
  - Analysis
  - Other
- Answer options:
  "High" (score=1; indicative of a low ROB)
  "medium" (score=2; indicative of a probably low ROB)
  "low" (score=3; indicative of a probably high ROB)
  "unacceptable" (score=4; indicative of a probably high ROB)
  - Not all answer options are available for each question

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ROB Judgments Using OHAT

	Detection Bias-Exposure Characterization	Selection Bias	Other Sources of Bias	Detection Bias-Outcome Characterization	Selective Reporting Bias	Confounding Bias	Attrition/ Exclusion Bias
Eskenazi et al. 2013	++	+	++	+	++	++	-
Chen et al. 2014	++	+	++	+	++	-	+
Roze et al. 2009	++	+	+	+	-	-	+
Adgent et al. 2014	++	+	++	+	++	-	-
Cowell et al. 2015	++	+	++	+	++	-	-
Hoffman et al. 2012	++	+	++	+	++	-	-
Gascon et al. 2011	++	+	+	+	++	-	-
Sagiv et al. 2015	+	+	++	+	++	-	-
Zhang et al. 2017	++	+	++	-	++	-	-
Herbstman et al. 2010	++	+	+	+	-	-	-
Shy et al. 2011	++	+	-	-	+	-	-
Gump et al. 2014	++	-	+	-	-	-	-
Gascon et al. 2012	++	+	++	+	++	-	--
Chao et al. 2011	+	+	+	-	--	-	-
Lin et al. 2010	++	+	-	-	--	-	-

Note: ++ indicates low, + indicates probably low, - indicates probably high, -- indicates high.

Eick, S.M., *et al. Syst Rev* **9,** 249 (2020). https://doi.org/10.1186/s13643-020-01490-8

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ROB Judgments Using TSCA

* Note does not account for the quantitative weighting of the different metrics

Dark green low ROB; Light green probably low ROB, Yellow probably high ROB; Red "unacceptable" probably high ROB)

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Using the TSCA methodology

	Statistical Power	Overall
Adgent et al 2014	4	4
Chao et al 2011	4	4
Chen et al 2014	4	4
Cowell et al 2015	4	4
Eskenazi et al 2013	4	4
Gascon et al 2012	4	4
Gascon et al 2011	4	4
Gump et al 2014	4	4
Herbstman et al 2010	4	4
Hoffman et al 2012	4	4
Lin et al 2010	4	4
Roze et al 2009	4	4
Sagiv et al 2015	4	4
Shy et al 2011	4	4
Zhang et al 2017	4	4

- All studies rated 'unacceptable' and removed from body of evidence due to Metric 13 "Statistical Power"
- "Medium" and "unacceptable" were only available answer options
- Judgement was based on instructions as written in TSCA tool
  - No available protocol

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Conclusions

- EPA IRIS also uses similar overall study quality ratings as USEPA TSCA tool.
  - <u>All studies excluded </u>from body of evidence.

- Risk of Bias evaluation is meant to provide consistency and transparency

- Quantitative scores and overall study quality ratings are arbitrary and not science-based
  - Can result in excluding important data

- Illustrates that consistency/transparency important – and methods matter
- Recommend using tools/methods that use validated, domain-based approaches which consider the entire body of evidence (e.g. OHAT, Navigation Guide)

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EPA CDR 2015; Woodruff et al 2011; National Cancer Institute 2010

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Study Question

Does developmental exposure to PBDEs in humans affect:
Quantitative measures of intelligence; or
**ADHD** and **attention-related behavioral conditions**?

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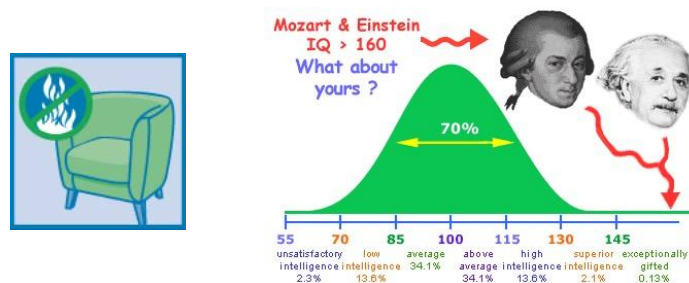
Result

- Fifteen studies met the inclusion criteria; 10 studies met the criteria for intelligence and nine for attention-related problems

- Studies of Intelligence: <u>Four studies </u>measuring BDE-47 in maternal serum during gestation or at birth or cord blood at birth and assessing FSIQ or MSCA in children 4–7 y old <u>were amenable to a meta-analysis</u>

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What's a few IQ points?
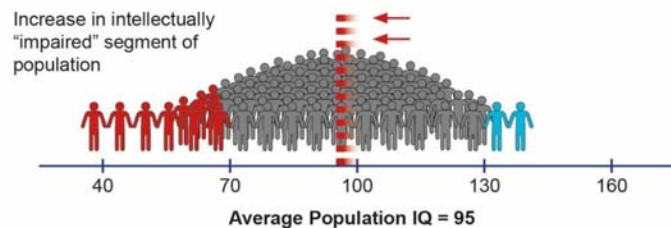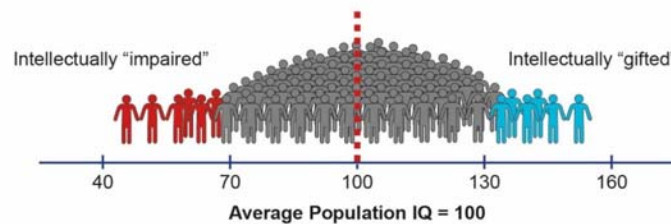
20

Comparison of Overall Study Quality Ratings

	Overall	
	IRIS	**TSCA**
Adgent et al 2014	-	4
Chao et al 2011	-	4
Chen et al 2014	-	4
Cowell et al 2015	-	4
Eskenazi et al 2013	-	4
Gascon et al 2012	-	4
Gascon et al 2011	-	4
Gump et al 2014	-	4
Herbstman et al 2010	-	4
Hoffman et al 2012	-	4
Lin et al 2010	-	4
Roze et al 2009	-	4
Sagiv et al 2015	-	4
Shy et al 2011	--	4
Zhang et al 2017	--	4

- Only IRIS and TSCA include indicators for overall study quality
  - All studies removed from body of evidence
- OHAT: approximately half of the studies had "low" or "probably low" ROB ratings across all domains
- Navigation Guide: most studies received ratings of "low" or "probably low" ROB across most domains
- No studies removed from overall body of evidence with OHAT or Navigation Guide

Note: For IRIS overall study confidence - indicates low. For TSCA 4/Red indicates 'unacceptable'

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PBDEs Significant Population Impacts

+43,000 cases
+$58 billion/ year

Distribution of intellectual abilities in US children

- IQ pts

70 IQ
6 million
Challenged

130 IQ
6 million
Gifted

Most of US

Credit: Bruce Lanphear
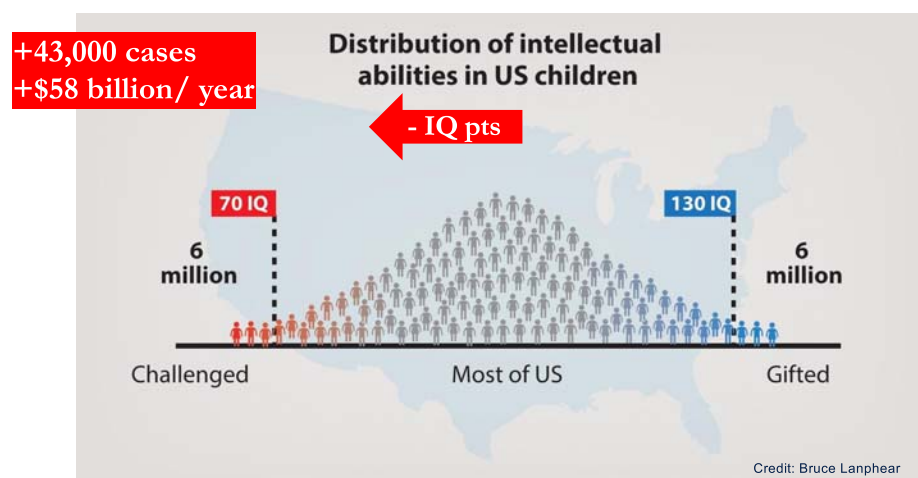
Attina 2016

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Other Results?

"A key challenge to our review was that many of the included studies were not combinable in a meta-analysis."

"Included ADHD studies generally reported association estimates on different scales or based on categories of exposures using different ranges, or they evaluated the health outcome at different life stages and with different assessment tools, leading us to conclude the data were too heterogeneous to be combined."

"Thus, we found limited evidence to determine whether there is a consistent relationship between PBDEs and ADHD."

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Evaluating Strength

CRITERIA:

1. **Quality of evidence:** Moderate
2. **What is the direction of effect?** Decrease in intelligence with increasing PBDE exposure
3. **What is the confidence in the effect?** A new study would be unlikely to change the certainty in the direction of the effect
4. **Are there other compelling attributes of the data that influence certainty?** None

?

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Systematic review of human evidence on PBDE exposure and IQ

EHP

CONCLUSION: "We concluded there was **sufficient evidence supporting an association** between developmental PBDE exposure and reduced IQ. Preventing developmental exposure to PBDEs could help prevent loss of human intelligence."

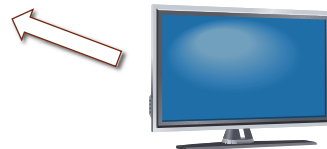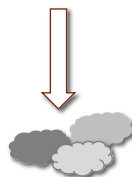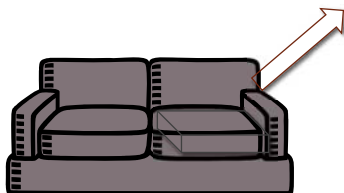| Every 10-fold increase in PBDE levels | associated with | Loss of 3.7 IQ points in children |

Lam, et al 2017

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Flame Retardants Continuously Migrate Out Of Products

① Not chemically bonded to plastic materials

② Chemicals off-gas Attach to particles in air

③ Contaminated particles settle in house dust

Weschler & Nazaroff 2008

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PBDE and IQ

A meta-analysis estimated 10-fold increase in exposure → 3.7 decrement in kid's IQ
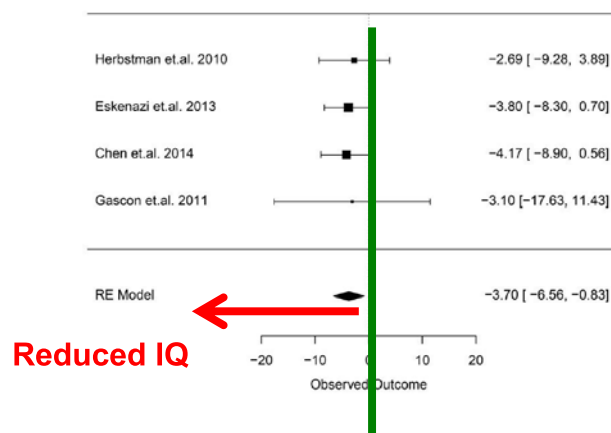
28

Epidemiological Studies: Human Health Associations

Main 2007; Akutsu 2008; Meeker 2009; Eskenazi et al, 2010, 2011, 2012

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Case Study

- Applied OHAT, TSCA, and IRIS tools to a previously published systematic review using Navigation Guide
  - Developmental PBDE Exposure and IQ/ADHD in Childhood: A Systematic Review and Meta-analysis - *Lam et al., 2017, EHP – found sufficient evidence for a relationship based on human studies*
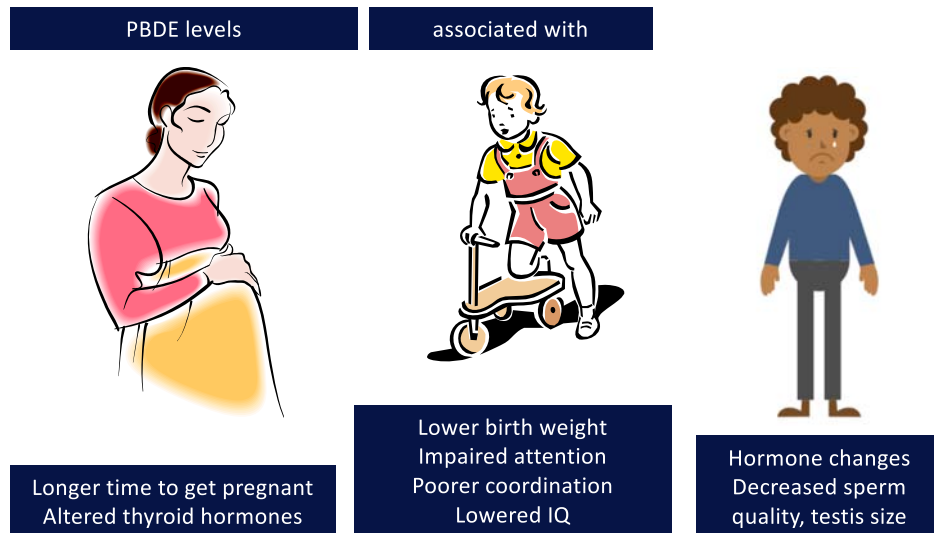 - *15* human epidemiologic studies
  - PBDE and IQ/ADHD systematic review was evaluated by the NAS *(Systematic Reviews Low Dose EDCs, 2017),* which concluded there was no evidence of bias in the assessment
  - Navigation Guide framework has been empirically demonstrated on six case studies, endorsed by the NAS
- Method
  - 2 reviewers completed training on assessing ROB using these tools
  - Reviewers applied each of the tools and independently rated each study
  - Tools applied using verbatim instructions provided in each tool
  - Tracked time to complete each ROB assessment for each tool
  - Kappa statistics calculated for each tool as measures of inter-rater reliability

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Brief Comparison of Tools

- The Navigation Guide, OHAT, IRIS, and TSCA tools all measure ROB due to :
  - Exposure and outcome measurement
  - Study population
  - Confounding
- IRIS and TSCA are the only tools that include indicators of overall study quality.

Tool	Assessment Process
OHAT	Risk of Bias, Internal Validity
IRIS	Study Evaluation
TSCA	Data Quality Criteria for Epidemiological Studies
Navigation Guide	Risk of Bias, Internal Validity

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ROB Navigation Guide

¤	Source Population Representation¤	Blinding¤	Exposure Assessment¤	Outcome Assessment¤	Incomplete Outcome Data¤	Selective Outcome Reporting¤	Confounding¤	Conflicts of Interest¤	Other Sources of Bias¤
Adgent·et·al.·2014¤	+¤	++¤	+¤	+¤	+¤	++¤	-¤	++¤	++¤
Chao·et·al.·2011¤	-¤	-¤	+¤	+¤	++¤	++¤	-¤	++¤	++¤
Chen·et·al.·2014¤	++¤	++¤	++¤	++¤	++¤	++¤	+¤	++¤	++¤
Cowell·et·al.·2015¤	+¤	++¤	+¤	+¤	-¤	++¤	+¤	++¤	++¤
Eskenazi·et·al.·2013¤	++¤	++¤	++¤	++¤	++¤	++¤	++¤	++¤	++¤
Gascon·et·al.·2012¤	++¤	++¤	++¤	++¤	++¤	++¤	+¤	++¤	++¤
Gascon·et·al.·2011¤	+¤	++¤	++¤	++¤	++¤	++¤	++¤	++¤	++¤
Gump·et·al.·2014¤	++¤	++¤	+¤	++¤	++¤	++¤	--¤	++¤	--¤
Herbstman·et·al.·2010·¤	+¤	++¤	+¤	+¤	-¤	++¤	+¤	++¤	++¤
Hoffman·et·al.·2012¤	-¤	-¤	++¤	-¤	+¤	--¤	-¤	++¤	++¤
Lin·et·al.·2010·¤	-¤	-¤	++¤	-¤	+¤	--¤	-¤	++¤	++¤
Roze·et·al.·2009¤	++¤	-¤	++¤	+¤	--¤	++¤	-¤	++¤	++¤
Sagiv·et·al.·2015¤	++¤	++¤	++¤	++¤	++¤	++¤	++¤	++¤	++¤
Shy·et·al.·2011¤	-¤	-¤	++¤	-¤	++¤	++¤	-¤	++¤	++¤
Zhang·et·al.·2017¤	++¤	++¤	++¤	++¤	++¤	++¤	+¤	++¤	++¤

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Tracey Woodruff, PhD, MPH

- Professor and Director, University of California, San Francisco Program on Reproductive Health and the Environment (UCSF PRHE)
- Former EPA scientist
- Leading expert on toxic chemicals, chemical policy, women & children's health
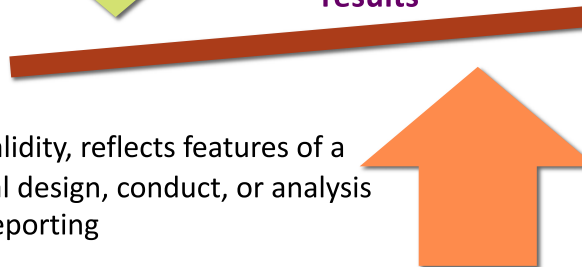- Overview of new TSCA and scientific concerns with EPA plans

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Risk of Bias

Characteristics of a study that can introduce systematic errors in the magnitude or direction of the results

- Measure of internal validity, reflects features of a study's methodological design, conduct, or analysis
- Different than study reporting

Higgins and Green 2011

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