International Conference on Using Epidemiological Studies in Health Risk Assessments: Relevance, Reliability and Causality

Berlin, November 09-10, 2023

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Impressum

BfR Abstracts

International Conference on Using Epidemiological Studies in Health Risk Assessments: Relevance, Reliability and Causality

The authors of the abstracts are responsible for the content.

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Contents

Ladies and gentlemen, esteemed guests, distinguished colleagues,

It is my great pleasure to welcome you all to the International Conference on Using Epidemiological Studies in Health Risk Assessments. This significant gathering, co-organized by the German Federal Institute for Risk Assessment (BfR) and the European Food Safety Authority (EFSA), is a platform for the exchange of knowledge and ideas at the intersection of health risk assessment and epidemiology. This is one priority area for many health institutions in reflection of the fact that not all problems in risk assessment can be solved alone on the basis of lab studies.

We have come together to emphasize the high relevance of human data in the field of health risk assessments. Epidemiological studies play a pivotal role in shaping our understanding of health risks across a wide spectrum, from food and feed safety, chemical and product safety, to occupational health, environmental health and animal health.

When carrying out evidence-based risk assessments, it is essential to assess evidence from observational epidemiological studies in conjunction with other sources of evidence, such as experimental animal studies. The weight-of-evidence approach provides a framework to integrate such disparate sources of information in a scientifically sound and comprehensive manner. However, this is not a simple undertaking.

First and foremost, it is important to foster interdisciplinary cooperation among the communities of risk assessment, epidemiology and particular scientific areas be it microbiology or toxicology. This involves getting everyone to talk to each other and trying to assess and combine all available evidence from different sources. Interdisciplinary cooperation is needed. This is also true when assessing epidemiological studies for risk of bias or evidence for causality which requires joined epidemiological and subject matter expertise.

There are some obstacles that must be overcome, and some of them may be based on misconceptions. For example, observational studies should not be dismissed from the risk assessment process merely because they cannot definitively prove causality.

The Brandenburg Gate, which is the image on the programme of this conference, can be passed freely in both directions for more than 30 years. Similarity, risk assessors and epidemiologists should come together and discover population health risks as their common terrain where both disciplines thrive and inspire each other.

We feel honoured to have convened 490 epidemiologists, health statisticians, risk assessors, and other professionals who utilize epidemiological evidence in their professional endeavours. Besides the interesting lectures, discussions and posters, we hope our social evening will also encourage getting to know each other and encourage informal discussions.

I am confident that this conference will be a resounding success in setting priorities, sharing experiences, insights, inspiring discussions and ideas to foster collaboration and innovation, and ultimately advance our fields.

I also hope that you will enjoy your stay in Berlin which is an interesting and vibrant city which can offer something for everyone, especially cultural events and science - we are in science week now - as well as good food and drink and other interesting aspects.

Thank you very much for joining us on this journey of knowledge and collaboration. I wish you all a very successful and fruitful meeting.

1 Programme

Thursday, 09 November 2023	
08:00–14:00	Registration
Pre-conference workshops	
09:00–10:30	**The OHAT approach for assessing risk of bias in epidemiological studies** Kyla W Taylor, Andrew A Rooney National Institute of Environmental Health Sciences, Durham, USA
10:30–12:00	**Epidemiological evidence in the context of risk assessment and introduction and usage of the raRoB tool** Sven Knüppel, Kristina Plate German Federal Institute for Risk Assessment (BfR), Berlin, Germany
12:00–13:00	Lunch break
Conference opening	
13:00–13:15	**Welcome** Tanja Schwerdtle Vice President of the German Federal Institute for Risk Assessment (BfR), Berlin, Germany Carlos Gonçalo das Neves Chief Scientist of the European Food Safety Authority (EFSA), Parma, Italy
Topic I: Using epidemiological studies in health risk assessments (Part 1)	
13:15–14:00	**Keynote 1:** **Epidemiology and risk assessment: reflections on working together to improve public health** Judy LaKind LaKind Associates, LLC, Catonsville, USA and University of Maryland-School of Medicine, Baltimore, USA
14:00–14:20	**Good practice occupational epidemiological systematic reviews – a recommendation paper** Janice Hegewald[1], Maria Girbig[2], Rebecca Wolf[1], Melanie Schubert[2], Ulrich Bolm-Audorff[2], Karla Romero Starke[2], Alice Freiberg[2], Andreas Seidler[2], on behalf of the „Gute Praxis arbeitsepidemiologische systematische Reviews“ (GPAR) working group [1]Federal Institute for Occupational Safety and Health (BAuA), Berlin, Germany [2]Technical University of Dresden, Germany

14:20–14:40	**Notes on the use of epidemiological and toxicological data for risk assessment** Emily A. McVey, Sylvia Notenboom, Guangchao Chen, Rik Bogers, Peter Engelfriet, Gerrit Wolterink, Annemieke Spijkerman, Astrid Bulder National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands
14:40–15:00	**Diminished semen quality following early exposure to persistent organic pollutants (POPs) as critical effect in health risk assessment?** Klaus Abraham[1], Deborah Kurz[2], Tanja Schwerdtle[1], Cornelia Weikert[1], Dietrich Rothenbacher[2] [1]BfR, Berlin, Germany [2]University of Ulm, Germany
15:00–15:45	Coffee break
Topic I: Using epidemiological studies in health risk assessments (Part 2)	
15:45–16:30	**Keynote 2:** **Opportunities and challenges of using epidemiological studies in health risk assessment from an IARC perspective** Joachim Schüz International Agency for Research on Cancer (IARC/WHO), Lyon, France
16:30–16:50	**Use of epidemiological data in microbiological risk assessments: two case studies from the UK Food Standards Agency** Erica Kintz Food Standards Agency, London, UK
16:50–17:10	**Use of epidemiological studies in a benefit and risk assessment of fish intake by the Norwegian Scientific Committee for Food and Environment (VKM)** Lene F Andersen[1,2], Helle K Knutsen[2,3], Bente Mangschou[2], Christine L Parr[2] on behalf of the Norwegian Scientific Committee for Food and Environment (VKM) project group, and VKM Scientific Steering Committee [1]University of Oslo, Norway [2]Norwegian Scientific Committee for Food and Environment (VKM), Oslo, Norway [3]The Norwegian Institute of Public Health, Oslo, Norway
17:10–17:30	**Use of epidemiological studies to assess nutritional risk of vegetarian diets** Perrine Nadaud[1], Sabine Houdart[1], Emmanuelle Kesse-Guyot[2] [1]French Agency for Food, Environmental and Occupational Health & Safety, Maisons-Alfort, France [2]Université Sorbonne Paris Nord, France

Closing of day 1	
17:30–18:00	**Brief statements** Susan Jebb, chair of the United Kingdom's Food Standards Agency (FSA) Antonio Hernández Jerez, chair of the EFSA PPR Panel Full & Department of Legal Medicine and Toxicology, Faculty of Medicine University of Granada Thorhallur Halldorsson, School of Health Sciences, University of Iceland & chair of EFSA working group on appraisal and integration of evidence from epidemiological studies
18:00–22:30	**Social evening: Get together (at conference venue)**

Friday, 10 November 2023	
08:00	Registration
Topic II: Critical appraisal of individual epidemiological studies (Part 1)	
08:30–09:15	**Keynote 3:** **Assessing risk of bias in estimates of the effects of exposures: the ROBINS-E tool** Julian PT Higgins Bristol Medical School, UK
09:15–09:35	**Application feature improvements in support of human health assessments: optimisations for epidemiology data extraction** Sean Watford[1], Krista Y. Christensen[1], Elizabeth Radke[1], Andy Shapiro[2] [1]US Environmental Protection Agency, Washington, DC, USA [2]US Environmental Protection Agency, Research Triangle Park, USA
09:35–09:55	**Probability bounds analysis as a way open up for semi-automatic quantification of bias terms in RoB – adjusted evidence synthesis** Ullrika Sahlin Lund University, Sweden
09:55–11:25	**Poster session and Coffee break**
Topic II: Critical appraisal of individual epidemiological studies (Part 2)	
11:25–12:10	**Keynote 4:** **Assessing the certainty in a body of evidence for studies addressing the effect of an exposure on an outcome** Holger Schünemann McMaster University, Hamilton, Canada and Cochrane Canada

12:10–12:30	**The OHAT approach to assessing risk-of-bias in individual epidemiological studies to support evidence integration and public health decision making** Kyla W Taylor, Andrew A Rooney National Institute of Environmental Health Sciences, Durham, USA
12:30–12:50	**A tool for rapid assessment of risk of bias (raRoB) in observational epidemiologic studies** Kristina Plate[1], Sven Knüppel[1], Narges Ghoreishi[1], Anselm Hornbacher[1], Kerstin Schmidt[2], Henning Thole[3], Christine Müller-Graf[1], Matthias Greiner[1] [1]BfR, Berlin, Germany [2]BioMath GmbH, Rostock, Germany [3]National Association of Statutory Health Insurance Physicians, Berlin, Germany and SRH University of Applied Health Sciences, Gera, Germany
12:50–14:00	Lunch break
Topic III: Appraising the epidemiological evidence on causality (Part 1)	
14:00–14:45	**Keynote 5** **Cause or correlation? – the case of air pollution** Barbara Hoffmann Heinrich-Heine-University of Düsseldorf, Germany
14:45–15:05	**Surveying the epidemiology evidence: examples of triangulation from the IRIS program** Krista Y Christensen, Rebecca Nachman, Thomas Bateson, Elizabeth Radke-Farabaugh Center for Public Health and Environmental Assessment, Washington, DC, USA
15:05–15:25	**Epidemiological results on pesticides and cancer, just a matter of p values and confounding?** Pierre Lebailly[1], Isabelle Baldi[2] [1]Centre François Baclesse, Caen, France and University of Caen Normandy, France [2]University of Bordeaux, France
15:25–16:10	Coffee break

Topic III: Appraising the epidemiological evidence on causality (Part 2)	
16:15–17:00	**Keynote 6** **Proper construction and interpretation of statistics for causality assessment and policy input** Sander Greenland University of California, Los Angeles, USA
17:00–17:20	**The UK Committees on Toxicity (COT) and on Carcinogenicity (COC) of chemicals in foods, consumer products and the environment: guidance for synthesising and integration of epidemiological and toxicological evidence** Barbara Doerr[1], Alan Boobis[2] [1]Food Standards Agency, London, UK [2]Imperial College London, UK
Panel discussion and conclusion	
17:20–18:10	**Panel discussion** Selected speakers and Dieter Schrenk, chair of the EFSA Panel on Contaminants in the Food Chain
18:10	**Concluding remark** Matthias Greiner BfR, Berlin, Germany
18:15	Conference closing

2 Abstracts - presentations

2.1 Epidemiology and Risk Assessment: Reflections on Working Together to Improve Public Health

Judy S. LaKind[1,2]

[1]LaKind Associates, LLC, Catonsville, MD, USA
[2]University of Maryland-School of Medicine, Baltimore, USA

Environmental epidemiologic research provides invaluable information for understanding the relationship between environmental exposures and health outcomes. Chemical risk assessment, a foundation of public health decision-making, relies on information from various disciplines including epidemiology. While epidemiology and risk assessment have common goals of understanding and reducing human health impacts associated with exposure to environmental chemicals, each discipline utilizes different terminologies and skill sets. This can make it difficult for public health officials to use epidemiology research for decision-making. For over twenty years, scientists have recognized that dialogue between risk assessors and epidemiologists is crucial, yet to date no specific path forward has been developed for this purpose. In this presentation, two tools designed to improve the utility of epidemiology research for use in risk assessment (and weight of evidence assessments) will be described. The first (BEES-C) focuses on data quality within the exposure assessment component of an epidemiology study. The other (the Matrix) is an educational tool with the goal of informing epidemiologists regarding the kinds of information needed for risk assessment. Some of these needs can be met during the study design and reporting phases, while others can be addressed post hoc. The Matrix includes a small number of "asks", thereby focusing the dialogue between epidemiologists and risk assessors; it covers key and complex components of any epidemiology study. Neither the Matrix nor the BEES-C are intended to supplant best practices for environmental epidemiology or existing frameworks on integrating multidisciplinary data. Rather, the goal to improve understanding and communication between the disciplines. Bridging the gap between epidemiology and risk assessment enriches both disciplines and enhances public health decision-making.

2.2 Good practice occupational epidemiological systematic reviews – a recommendation paper

Janice Hegewald[1], Maria Girbig[2], Rebecca Wolf[1], Melanie Schubert[2], Ulrich Bolm-Audorff[2], Karla Romero Starke[2], Alice Freiberg[2], Andreas Seidler[2], on behalf of the „Gute Praxis arbeitsepidemiologische systematische Reviews“ (GPAR) working group

[1]Federal Institute for Occupational Safety and Health (BAuA), Berlin, Germany
[2]Technical University of Dresden, Germany

Evidence-based methods are often used to summarize and appraise the results of observational studies in occupational settings. While the evidence synthesized from systematic reviews is used to inform occupational prevention practice, legislation, and implementation (e.g., in occupational disease legislation or for setting prevention thresholds), established evidence-based methods developed for the systematic identification, collection, synthesis, analysis, and appraisal of clinical research are not always applicable or practical for human health risk assessments in occupational settings. Recommendations are therefore needed on how best to adapt and apply evidence-based methods to occupational research.

In 2022, a working group of more than 20 scientists was formed to evaluate research methods and consider how best to adapt them to the issues of the world of work. The goal of the working group is to develop and publish recommendations.
The working group is divided into subgroups to focus on each phase of a systematic review:
1) Literature search/screening (led by Maria Girbig and Rebecca Wolf).
2) Data extraction (led by Melanie Schubert)
3) Risk of bias (led by Ulrich Bolm-Audorff)
4) Meta-analysis (led by Karla Romero Starke)
5) Evidence assessment (led by Alice Freiberg)

The recommendations contained in this document are intended to provide guidance for improving the quality and comparability of future systematic reviews on occupational safety and health risk assessments.

2.3 Notes on the use of epidemiological and toxicological data for risk assessment

Emily A. McVey, Sylvia Notenboom, Guangchao Chen, Rik Bogers, Peter Engelfriet, Gerrit Wolterink, Annemieke Spijkerman, Astrid Bulder

National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

The RIVM Epitox workgroup began in 2019 with an eye towards bringing epidemiologists and toxicologists within the Agency together to work on risk assessments and to share experiences and knowledge across the fields. Since that time, the group has analyzed past case studies for important experiences and information that can be shared moving forward. Our goal in doing this is to smooth the process of evaluating and integrating all data and provide the most certain and appropriate risk assessment for the case in question, as well as advise future study design. Specific studies or risk assessment cases may be proposed for discussion. In addition, the group serves as a source for other toxicologists and epidemiologists within the Agency for better understanding of studies and data from each silo. Currently, the group is working on tips and tricks for toxicologists and epidemiologists within the Agency for everything from study design to study evaluation. We are also analyzing several recent case-studies and brain-storming ways to combine/weigh toxicological and epidemiological data in a more quantitative manner.

2.4 Diminished semen quality following early exposure to persistent organic pollutants (POPs) as critical effect in health risk assessment?

Klaus Abraham[1], Deborah Kurz[2], Tanja Schwerdtle[1], Cornelia Weikert[1], Dietrich Rothenbacher[2]

[1]BfR, Berlin, Germany

[2]University of Ulm, Germany

Diminished semen quality especially in Western countries is under discussion since decades ("male fertility crisis"). In epidemiological studies, many life style factors have been found to be associated, but also environmental contaminants have been suspected. Regarding the latter, some of the persistent organic pollutants (POPs) may impact the early development of the male reproductive system, e.g. during the mini-puberty at the age of about three months. One of the POPs suspected are polychlorinated dibenzo-p-dioxins (PCDDs, "dioxins"), as early exposure to high doses has been shown to reduce the semen quality in rodents. With respect to humans, evidence comes from high dose exposure to the most potent dioxin (TCDD) following the Seveso accidence in 1976. For its risk assessment on dioxins in 2018, EFSA has identified diminished semen quality in adulthood following pre- and postnatal exposure as critical effect. The Authority used an investigation of 9-year old boys from a Russian industrialized city as key study. As documented in the process of public consultation, BfR was not convinced by the EFSA approach.

In 2022, a Danish study by Hærvig et al. focusing solely on prenatal exposure to a different POP group, namely per- and polyfluorinated alkyl substances (PFAS), reported similar associations with parameters of semen quality, but neither investigated nor discussed dioxin exposure. However, dioxin and PFAS exposure are correlated (r=0.77 at the end of the first year of life: Abraham, EHP 2023).

To shed more light on the matter, we have initiated a study based on the population based longitudinal Ulm Birth Cohort with baseline recruitment in 2000/01. Male participants invited in 2021/22 provided at least one semen sample. Estimation of early dioxin and PFAS exposure (by analysis of stored mother's milk and serum samples, respectively) will allow simultaneous assessment of the relationships of both, dioxins and PFAS, with semen quality.

2.5 Opportunities and challenges of using epidemiological studies in health risk assessment from an IARC perspective

Joachim Schüz
International Agency for Research on Cancer (IARC/WHO), Lyon, France

The International Agency for Research on Cancer (IARC) is the specialized cancer research agency of the World Health Organization (WHO), with the main objective of promoting international collaboration in cancer research. With the emphasis on cancer prevention IARC focuses on four key questions: 1) "Data for Action: who develops cancer, where, and when?" through collecting and curating the world's cancer data, to study the magnitude and patterns of cancer worldwide; 2) "Understanding the causes: why do people develop cancer?" through elucidating the role of environmental and lifestyle risk factors and studying their interplay with genetic background in population-based studies, reflecting the understanding that most cancers are caused by modifiable risk factors; 3) "From Understanding to Prevention: how can we prevent cancer effectively?" through evaluating different types of interventions such as behaviour change, screening, and vaccination, to determine what works best in different settings; 4) "Knowledge Mobilization: how can we mobilize and share our knowledge?" through authoritative sources of information provided to the international cancer control community. Cancer prevention becomes even more important as IARC projects the annual global cancer burden to increase from about 20 million per year today to 30 million per year in about 20 years time, due to the demographic changes of aging populations and cancer becoming more common with increasing age; this cancer burden cannot be tackled with treatment alone, not even by the most affluent countries.

From the scope of work it is easily understandable that several of the IARC tasks are related to cancer risk assessments or systematic reviews of the scientific evidence. The IARC Monographs program on the Identification of Carcinogenic Hazards to Humans runs for over 50 years and has evaluated more than 1,000 agents with respect to their carcinogenicity (1). For this purpose human data (epidemiological studies), animal experimental studies, and mechanistic data are evaluated and the three lines of evidence combined in an overall evaluation; of all evaluations 127 agents have been classified as carcinogenic, with another over 400 agents as probably or possibly carcinogenic. The IARC Handbooks of Cancer Prevention evaluate what works in cancer prevention, with the most recent one on oral cancer prevention (2). Within the World Code against Cancer Framework program, the knowledge on what causes cancer and what preventive measures exist is translated into recommendations to the general public and to policy-makers on how to reduce the risk of developing cancer. Codes are developed by region to reflect differences in cancer and in risk factor patterns, and at present exist for Europe (3) and for Latin America and the Caribbean (4). Risk assessments are sometimes carried out on requests of member states for specific questions, like the development of recommendations on thyroid screening after nuclear accidents (4). All IARC assessments have in common that results from epidemiological studies play a major role in the evaluations, acknowledging that this is the research in the target population under real-life conditions and thereby most directly relevant for developing cancer prevention strategies.

Importantly, the risk of bias assessment has to start at the level of the individual study and is therefore routinely implemented in IARC's research consortia as well as the conduct of studies with IARC involvement. This is because only access to the raw data allows extensive sensitivity analyses using data from validation studies or modelling various error scenarios. IARC urges that for state-of-the-art cancer epidemiology pilot studies and validation studies that allow risk-of-bias assessments are indispensable. Epidemiological studies always suffer from measurement error and bias, but this does not necessarily lead to flawed estimations of the dose-response relationship between exposure and outcome. An example is studies on the association between mobile phone use and the risk of brain tumours, for which cohort studies with relatively

crude exposure information showed no association but the major case-control study with detailed but self-reported exposure information showed a J-shaped relationship, with biologically implausible results for low and ordinary mobile phone use as the observed association was inverse, and inconsistent but positively associated results in very heavy mobile phone users (5). Thanks to the conduct of carrying out several validation studies, including use of non-responder questionnaires, comparing self-reported past and contemporary use with mobile phone operator traffic data, and plausibility checks with incidence rate time trends the interplay of measurement error, exposure misclassification, selection bias and confounding was better understood and reveals that with respective adjustment for error the consistency with the cohort study results of no association appears to be the most likely explanation (6).
In conclusion, IARC strongly supports the use of findings from epidemiological studies in any health risk assessment. Critical appraisal of bias is key to distinct between causal, coincidental, and spurious associations. Assessment of study quality has to be comprehensive at the level of the individual study with access to the raw data, as the risk-of-bias toolkits used in systematic reviews can only be as good as how transparent and comprehensive bias from the original studies is reported. At present, epidemiology faces even additional challenges, such as lack of motivation of European citizens to participate in studies, the General Data Protection Regulation (GDPR) which shows more and more how (unintentionally) damaging it is for epidemiology, and the lack of funding schemes that include proper conduct of risk-of-bias assessments in individual studies.

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(2) Bouvard V, Nethan ST, Singh D, et al. IARC Perspective on Oral Cancer Prevention. N Engl J Med 2022; 387(21):1999-2005. doi: 10.1056/NEJMsr2210097.
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(4) Espina C, Feliu A, Maza M, et al. Latin America and the Caribbean Code Against Cancer 1st Edition: 17 cancer prevention recommendations to the public and to policy-makers (World Code Against Cancer Framework). Cancer Epidemiol 2023;86 Suppl 1:102402. doi: 10.1016/j.canep.2023.102402.
(5) INTERPHONE Study Group. Brain tumour risk in relation to mobile telephone use: results of the INTERPHONE international case-control study. Int J Epidemiol 2010; 39(3):675-94. doi: 10.1093/ije/dyq079.
(6) Deltour I, Poulsen AH, Johansen C, et al. Time trends in mobile phone use and glioma incidence among males in the Nordic Countries, 1979-2016. Environ Int 2022; 168:107487. doi: 10.1016/j.envint.2022.107487.

2.6 Use of epidemiological data in microbiological risk assessments: two case studies from the UK Food Standards Agency

Erica Kintz
Food Standards Agency, London, UK

As the government department responsible for ensuring food and feed safety, the UK Food Standards Agency conducts risk assessments to inform decisions about potential changes to legislation, food business guidance, or consumer advice. These assessments may incorporate or refer to epidemiological data including sequence-based inferences of transmission pathways and information about vulnerable groups derived from observational studies or historical outbreak reports. Two examples are discussed here.

The first assessed the risk to vulnerable populations from consuming ready-to-eat smoked fish. Vulnerable populations considered included pregnant women, the immunocompromised and the elderly. A literature search was performed to identify outbreaks caused by this food/pathogen combination. The UK Health Security agency provided evidence of human cases that had been linked by whole genome sequencing (WGS) and food history data to smoked fish food isolates. These two datasets supported separate risk characterisations for hot and cold smoked products, which in turn will allow consumer advice to be tailored to cold-smoked fish.

In the second risk assessment, the risk of acquiring avian influenza from poultry meat and poultry products was assessed. Literature searches did not identify any direct epidemiological evidence of foodborne transmission, although several sources described cases of infection after consuming raw blood, reported in 2005. The absence of reports implicating foodborne exposure to avian influenza despite the volume of literature searched was a factor in determining a negligible to very low risk of acquiring avian influenza from consuming cooked or less than thoroughly cooked poultry products.

These two examples illustrate how epidemiological evidence, or the lack of it, can impact the risk characterisation in microbiological risk assessments.

2.7 Use of epidemiological studies in a benefit and risk assessment of fish intake by the Norwegian Scientific Committee for Food and Environment (VKM)

Lene F. Andersen[1,2], Helle K. Knutsen[2,3], Bente Mangschou[2], Christine L. Parr[2] on behalf of the Norwegian Scientific Committee for Food and Environment (VKM) project group, and VKM Scientific Steering Committee
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[2]Norwegian Scientific Committee for Food and Environment (VKM), Oslo, Norway
[3]The Norwegian Institute of Public Health, Oslo, Norway

In 2022, VKM published a comprehensive benefit and risk assessment commissioned by the Norwegian Food Safety Authority, to estimate health consequences if fish intake remains at current level or increases to meet national recommendations (available at VKM.no). Benefits were questioned after the European Food Safety Authority (EFSA) lowered the tolerable weekly intakes for dioxins (PCDD/Fs) and dioxin-like PCBs (dl-PCBs), and perfluorinated alkylated substances (PFASs).

VKM performed systematic literature reviews and meta-analyses of the epidemiological evidence for intake of fish (total, fatty, lean) and nutrients in fish, as risk factors for cardiovascular diseases, diabetes, hip fractures, cognition/mental health, neurodevelopment, birth outcomes, body composition, immune-related diseases, and male fertility/semen quality. The World Cancer Research Fund (WCRF) latest report was used for cancer, and the recent EFSA evaluations for PCDD/Fs and dl-PCBs, and PFASs, where the critical endpoints are semen quality and immune effects, respectively.

After eligibility screening, VKM critically appraised over 340 primary studies (270 included) and 154 systematic reviews (84 included), using templates adapted from the Nordic Nutrition Recommendations 2012 (primary studies) and AMSTAR (reviews). The evidence for causal effects was graded by WCRF criteria for “convincing”, “probable”, “limited, suggestive”, “limited, no conclusion”, or “substantial effect on risk unlikely”, based on pooled high-low risk estimates, dose-response meta-analyses, between-study heterogeneity, and plausible mechanisms. Results on fish intake, nutrients, and contaminants were also evaluated for consistency.

An important limitation was lack of studies on fish intake in relation to health outcomes critical for contaminants, and studies with mediation analyses, to assess if health effect of eating fish may differ from the separate effects of nutrients and contaminants for which fish is an important source.

2.8 Use of epidemiological studies to assess nutritional risk of vegetarian diets

Perrine Nadaud[1], Sabine Houdart[1], Emmanuelle Kesse-Guyot[2]

[1]French Agency for Food, Environmental and Occupational Health & Safety, Maisons-Alfort, France
[2]Université Sorbonne Paris Nord, France

Context:
The French Agency for Food, Environmental and Occupational Health & Safety (ANSES) is in charge of assessing scientific evidence to develop dietary recommendations that meet the nutritional needs of vegetarian populations.

Objective:
Using systematic reviews of epidemiological studies, ANSES is exploring the relationship between vegetarian diets (i.e. lacto-ovo-vegetarian and vegan diets) and health outcomes.

Method:
The electronic databases PubMed/Medline and Scopus were searched from inception to 29 May 2019. Using DistillerSR, 14700 references were dually screened using predetermined inclusion criteria. Each included article was extracted and the risk of bias was assessed using the Risk of Bias for Nutrition Observational Studies tool (RoB-NObs) or the Risk of Bias in Nonrandomized Studies - of -Interventions (ROBINS-I) tool. Strength of the evidence was qualified using the five grading elements of the NESR's grading rubric and a decision tree was developed by the working group.

Results:
A total of 144 articles were included. With the exception of the health outcome related to nutritional status, which allowed cross-sectional design (n=69), most studies were prospective cohort studies with large sample size. Several conclusions were drawn but high to moderate risk of bias, mainly due to confounding factors such as family history of disease, age, sex, smoking, physical activity and socioeconomic status, reduced the strength of the evidence.

Conclusion:
Epidemiological studies have enabled the assessment of the nutrition-related chronic disease risk of vegetarian diets. The decision tree developed by the working group allowed us to address the limitations inherent in the design of these studies in a systematic, reproducible, transparent and robust way.

2.9 Assessing risk of bias in estimates of the effects of exposures: the ROBINS-E tool

Julian PT Higgins
Bristol Medical School, UK

I will describe the Risk Of Bias In Non-randomized Studies of Exposures (ROBINS-E) tool, a new framework for thinking through threats to the validity of findings from an observational study of the effect of an exposure on an outcome. The tool was developed by an international collaboration of epidemiologists, systematic reviewers and statisticians, following principles adopted by previous, widely-used tools (including the RoB 2 tool for randomized trials and the ROBINS-I tool for non-randomized studies of the effects of interventions). ROBINS-E addresses seven domains of bias, including bias due to confounding, selection biases, measurement biases and bias in selection of the reported result. Judgements about risk of bias derived using the tool should be useful in evaluating the relative strengths and weaknesses of evidence from different sources.

2.10 Application feature improvements in support of human health assessments: optimisations for epidemiology data extraction

Sean Watford[1], Krista Y. Christensen[1], Elizabeth Radke-Farabaugh , Andy Shapiro[2]
[1]US Environmental Protection Agency, Washington, DC, USA
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Toxicity values derived for human health assessments are relied upon for decision making to protect human health and the environment. To increase efficiency and optimize resources required to review and extract relevant information from literature, systematic review methods are employed with tools that improve user interfaces and interactions (UI/UX); standardize data exchange formats; and utilize artificial intelligence for (semi-)automation.

The Health Assessment Workspace Collaborative (HAWC) is a content management system for human health assessments. Data extraction features are available for both animal toxicology and epidemiology studies. Data extractions are integrated with visualization capabilities and can be produced with minimal data processing. We describe recent updates made by the HAWC team in coordination with EPA epidemiologists to update data extraction features including updates to UI/UX and adding more flexibility of the available forms to accommodate partial extractions.

Forms for data extraction include: study design, chemicals, exposures and exposure levels, adjustment factors, outcomes, and quantitative results. The flexibility provided with these updates enables the development and storage of information for evidence maps, toxicological reviews, visualizations, and interoperability with other tools. For example, information can be automatically extracted using machine learning methods in a platform like Dextr and exported into HAWC. Dextr is a tool that allows users to apply machine learning models to semi-automate data extraction from full text.

HAWC continues to be the major content repository for human health assessments. The updates to HAWC epidemiology data extraction improves the efficiency at which information can be extracted from studies and readily incorporated into assessments. The updates also facilitate integration of external tools and methods.

2.11 Probability bounds analysis as a way open up for semi-automatic quantification of bias terms in RoB – adjusted evidence synthesis

Ullrika Sahlin
Lund University, Sweden

Qualitative judgements on risk of biases are helpful to select which studies to include or exclude in an evidence synthesis. Quantitative bias analysis opens up to adjust for risk of bias in the statistical model for the synthesis. Such quantitative bias modelling requires the specification of quantitative bias terms, and the exact values on these terms requires judgements based on the type of biases and studies involved, as they cannot be informed by the data going into the statistical model for the evidence synthesis. The influence of alternative bias term specifications can be studied by sensitivity analysis, e.g. with the purpose to see if the choices change the conclusion. Raices Cruz et al. (2022) proposed a semi-automatic approach to specify bias terms based on the type of qualitative judgements on risk of bias combing from typical frameworks for qualitative appraisal and risk of bias evaluation. Bias terms are quantified by intervals as opposed by single values, and in the framework sensitivity analysis is replaced by a probability bound analysis to assess lower or upper bounds on the relevant quantity of interest resulting from the impression in bias terms. The bias-adjusted statistical model for evidence synthesis is implemented into a framework for robust Bayesian inference, where imprecision in bias terms results in convex sets of likelihoods. In this presentation, the approach to use probability bounds analysis to open up for semi-automatic quantification of bias terms in quantitative bias analysis will be presented and demonstrated on a set of evidence synthesis examples.

Raices Cruz, I., Troffaes, M. C., Lindström, J., & Sahlin, U. (2022). A robust Bayesian bias-adjusted random effects model for consideration of uncertainty about bias terms in evidence synthesis. Statistics in Medicine, 41(17), 3365-3379.

2.12 Assessing the certainty in a body of evidence for studies addressing the effect of an exposure on an outcome

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The abstract was not available at the time of printing.

2.13 The OHAT approach to assessing risk-of-bias in individual epidemiological studies to support evidence integration and public health decision making

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Systematic review methods present the essential framework for rigorously and transparently drawing causal inference for evidence-based decision making. These methods have become the standard in developing environmental health hazard assessments, which are routinely relied upon by governmental and international agencies to identify and evaluate chemical hazards, establish evidence-based guidelines, and inform critical public health decisions. The evidence base used in many of these assessments include diverse sources of information of varying quality. Therefore, it is imperative that literature-based evaluations assess the credibility of individual studies used to reach conclusions through consistent, transparent, and accepted methods. The OHAT systematic review framework addresses study credibility by assessing internal validity or “risk of bias”- the assessment of whether the design and conduct of a study compromised the credibility of the association between exposure and outcome. The OHAT risk-of-bias tool for individual studies is unique in its parallel approach to evaluating risk-of-bias from epidemiological and experimental animal studies to facilitate the integration of evidence and inform causality. This approach uses common domains and terminology to arrive at a risk-of-bias judgement for each specific type of potential bias. The types of biases that are assessed include selection bias, information bias (performance and detection bias- measurement error, outcome and exposure misclassification), attrition bias, reporting bias, and potential confounding. Expert reviewers use this tool to carefully evaluate individual studies for the potential for bias, and if possible, the magnitude and direction of the bias, using transparent guidelines outlined in the protocol that are tailored to the specific exposure and outcome of interest. Examples from previous and current literature-based evaluations will be used to demonstrate how the OHAT approach supports the development of confidence and hazard conclusions by allowing for comparison of particular risk-of-bias issues across a body of evidence and facilitating comparison of the strengths and weaknesses of different bodies of evidence.

2.14 A tool for rapid assessment of risk of bias (raRoB) in observational epidemiologic studies

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There are already numerous instruments for assessing the evidence from individual epidemiological studies, mostly in the course of systematic reviews. Special attention is given to the assessment of systematic errors (bias). However, the available instruments are limited in their applicability. These often focus on interventional studies, which examine planned interventions in a controlled setting. In contrast, there are few established instruments for observational epidemiological studies, which address exposures under real-world conditions and thus are relevant in the field of risk assessment. Most established instruments are also very complicated to use, require specialized training, and the application process is time-consuming due to the complexity of the assessment.
In order to enable also a rapid assessment of the risk of bias in epidemiological observational studies, we developed and tested a suitable instrument, the raRoB tool (rapid assessment of Risk of Bias).
During the development, an extensive search was conducted first for methods to assess the risk of bias, resulting in 152 identified strategies. The corresponding items and domains were extracted and systematized. Consistently occurring assessment items were then implemented in a dialog-oriented and user-friendly manner in a software tool, which was tested in a pilot study (among epidemiologists and statisticians) and two test phases (among scientists in the context of risk assessment). Based on the test results and rater feedback, the tool was revised and improved.
Applications addressed include recent publications of human studies on health risks that need to be assessed in the short term. The content and structure of the tool have therefore been chosen so that it can be applied by scientific experts without specific epidemiological knowledge for a rapid and handy assessment of the risk of bias.

2.15 Cause or correlation? – the case of air pollution

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The abstract was not available at the time of printing.

2.16 Surveying the epidemiology evidence: examples of triangulation from the IRIS program

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'Triangulation' refers to the integration of results from different approaches taken to address a research question. If each approach has different intrinsic sources of potential bias, comparing their results may reduce uncertainties in the overall body of evidence. For chemical health assessments, triangulation may be applied within a single study, within a single stream of evidence (e.g., synthesis of all epidemiologic studies), or across evidence streams (e.g., integration of toxicological, epidemiologic, and mechanistic). Application of triangulation to integrate across evidence streams is an established approach in US EPA risk assessment, but there is a need to develop systematic and transparent approaches for applying triangulation within and across epidemiologic studies. Here, we describe three examples of triangulation of epidemiological evidence from the Integrated Risk Information System (IRIS) program of the US EPA. In the first example from the Libby amphibole asbestos (LAA) IRIS assessment, there was concern that uncontrolled confounding by smoking could influence the observed risk estimate for LAA and lung cancer. Since the occupational cohort did not have complete smoking information, the potential for such confounding was evaluated using a negative control outcome. In the second example, from the IRIS evaluation of trichloroethylene and cancer, there was concern that co-exposures and uncontrolled confounding could influence observed effects. Methods based upon meta-analysis and grouping or stratification of studies, were used to evaluate these concerns. The third example is the draft IRIS evaluation of the association of formaldehyde exposure and cancer. Again, major concerns were co-exposures and uncontrolled confounding, which were investigated by comparing results by study population and exposure setting. These examples from the IRIS program demonstrate triangulation within an evidence stream (epidemiology) to support causal conclusions.

2.17 Epidemiological results on pesticides and cancer, just a matter of p values and confounding?

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Over the past decades, epidemiology has been able to identify causes of many diseases and thus contributed in huge progress in Public Health. However, the notion of causality between an exposure and a disease remains a subject of debates especially for multifactorial chronic diseases like cancer, and is frequently questioned by scientists from other disciplines. Causality is not limited to the notion of statistical significance of an association between a factor and a disease. It goes far beyond the framework of biostatistics by taking on board many other considerations, the principles of which were set out by Sir Bradford Hill more than 50 years ago and whose application requires a very good knowledge of epidemiological methods and research contexts. In the context of occupational exposure, where the priority is to detect risks in order to make decisions and remove workers as quickly as possible from situations that are harmful to their health, the notions of association and causality must be used very differently from other contexts, such as clinical research. To illustrate this, we will rely on some specific results from the multidisciplinary work conducted in France by us among farmers with the large AGRICAN agricultural cohort, which is following more than 180,000 agricultural workers for nearly 20 years to assess the links between their work and their diseases and with field studies used to measure pesticide exposure in various agricultural contexts (vineyard, open field, livestock, fruit growing, green spaces…) and tasks (pesticide application, re-entry, harvesting, sowing…). We will show how this approach provides causality arguments on the link between exposure to pesticides and certain cancers and the way these results should be interpreted and used based on more than 23,000 incident cancers (4,700 prostate cancer, 2,200 breast cancer and 2,000 lymphomas) and more than 500 days of observations with pesticide measurement under usual conditions of work.

2.18 Proper construction and interpretation of statistics for causality assessment and policy input

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We need to learn how to systematically deal with and teach about cognitive biases as we have done with mechanical biases like confounding. These biases are larger, more pervasive and socially more important than recognized in current methodologic texts and literature. Their coverage deserves to displace many finer points of statistical methodology, which itself is a source of cognitive biases. Almost no statistical analysis accounts for all sources of uncertainty about inferential targets (such as effects). This failure often causes overstatement of conclusions. Most statistics primers and study reports suffer from misinterpretation of already unrealistic statistical results. The resulting mistakes get amplified in discussions, reviews, and press coverage. Often, motivated reasoning determines the direction of errors and biases.

2.19 The UK Committees on Toxicity (COT) and on Carcinogenicity (COC) of chemicals in foods, consumer products and the environment: guidance for synthesising and integration of epidemiological and toxicological evidence

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The UK Committees on Toxicity and on Carcinogenicity reviewed current practice how different evidence streams should be integrated in chemical risk assessment and developed applicable guidance how best to achieve this in a transparent manner, giving appropriate weight to all evidence.

The decision-making process should be robust, transparent, evidence-based, defensible and documented but equally importantly, it should be easy to use. Collaboration and ongoing dialogue between epidemiologists, exposure experts and toxicologists are strongly advised. Information on mode of action can be invaluable for evidence integration as it underpins weight of evidence considerations by providing the mechanistic link between empirical observation and biological plausibility.

All lines of evidence should be considered, with no specific hierarchy a priori. One way to clearly depict the consensus conclusion on the influence of the different lines of evidence on the null hypothesis of causality is via visual representation. Decisions on whether there is sufficient information to reach a conclusion or whether a causal relationship in humans is more likely or less unlikely can be reached based on where the causal interference appears on a graph. The impact of the different lines of evidence is influenced by several factors, including strength or weakness in the data, the relative weighing of epidemiological and toxicological studies and uncertainties associated with the data. When more information is added and/or becomes available the placement of the toxicological and/or epidemiological evidence can be easily adjusted and a determination made whether the conclusion remains valid or should be changed. An estimate of the overall uncertainty should be included and, where appropriate, guidance on how data gaps could be filled.

The Committees recognised that issues on which their advice is sought vary considerably and hence the guidance proposed had to be sufficiently flexible to address this.

3 Abstracts - poster

3.1 Integrating epidemiological data in human health risk assessment: What risk assessors told us they need

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Environmental epidemiology has proven critical to evaluating various associations between environmental exposures and adverse human health effects. However, there is a perception that it does not sufficiently inform quantitative risk assessment. To help address this concern, the Health and Environmental Sciences Institute initiated in 2017 a project engaging the epidemiology, exposure science, and risk assessment communities with tripartite representation from government agencies, industry, and academia in a dialogue on the use of environmental epidemiology for quantitative risk assessment.

The committee sought to collect feedback from risk assessors regarding their use of epidemiological data. To better understand the practical needs risk assessors may have regarding epidemiological data, we deployed a survey that explored how much they used or may wish to use epidemiology studies for their assessments, and what might help them make epidemiological data more central to their work.

Preliminary analysis of the collected responses reveal that risk assessors would welcome more rigorous exposure evaluations in epidemiological studies, as well as greater emphasis on improved dose-response information, a more thorough evaluation of confounders, and overall increased transparency of study protocols and data reporting, as well as a more critical appraisal of the meaning of study results by epidemiologists. They call for greater collaboration of epidemiologists with toxicologists and cautioned about the over-interpretation of incompletely reported epidemiologic results. We propose actionable steps that should realize the full potential of human data in risk assessment.

3.2 Slovenian experience in using human biomonitoring data of exposure to chemicals in risk assessment

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The Slovenian National Institute of Public Health is responsible for comprehensive risk assessment (RA) for human health with over 20 years of experience including RA based on human biomonitoring (HBM) data.
We assessed risk to health of children and/or adults based on HBM data on exposure for the following chemicals inorganic and total arsenic (iAs, tAs), copper (Cu), glyphosate, lead (Pb) and persistent organic pollutants (POPs), i.e. the sum of tetrachlorodibenzodioxins/furans and dioxin like polychlorinated biphenyls. The following were used as points of departure: for iAs and tAs in non-cancer RA the biomonitoring equivalent (BE) of 6.4 µg/L (urine), for Cu in adults 2000 µg/L (blood) and 60 µg/L (urine), for gylphosate the Acceptable Daily Intake of 0,5 mg/kg/day, for Pb the Benchmark Dose Levels of blood Pb in adults for the elevated systolic blood pressure (150 µg/L), for POPs BE of up to 0.9 pg/g fat (human milk). The cancer burden from As and glyphosate was estimated by analysing the Cancer Registry data.
The exposure to As and glyphosate did not present risk to health of children or adults, nor did the exposure of adults to Cu or Pb. The cancer burden estimate did not show an increased risk for children living in As polluted area, nor accumulation of cancer cases in the area with production of glyphosate based herbicides. The exposure of infants to POPs via maternal milk significantly exceeded the current BEs for the selected POPs, thus indicating a risk. A possible area for intervention could be mothers' diet. The geometric mean for Pb in blood of children in the most Pb polluted area was 32.55, the 95th percentile 104 µg/L. In the absence of safe levels of Pb adherence to exposure reduction measures was recommended.
We advocate that the advancement of systematically designed and executed HBM studies contributes to high quality epidemiological data and presents an important long-term contribution to the 3R (reduction, refinement, replacement) strategy in RA.

3.4 Using epidemiologic data in the development of Occupational Exposure Limits: An Industry Perspective

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Maintaining safe operations and protecting worker health is a priority for ExxonMobil (EM). One of the resources used in industry to ensure worker safety is the establishment and maintenance of occupational exposure limits (OELs). As such, EM maintains a formal internal procedure for setting science-based, data driven OELs. This presentation will describe the best practices and challenges for using human data in health risk assessment for the purpose of developing a protective OEL. Specifically, when human data are the sole source of evidence, when animal data are the basis even though epidemiologic data are available, and what are the reasons for the above choices. Finally, this presentation will describe the characteristics of epidemiologic studies that are having the potential to be informative to determining an OEL value. Specific examples will be used for illustration during the presentation.

Observational epidemiology studies are commonly used to assess human health effects for occupational exposures and can inform hazard characterization or serve as supportive studies. Analytical epidemiology studies with specific characteristics (e.g., quantitative exposure data, confounding addressed, appropriate time window of exposure, accurate dose response) have the highest potential to inform an OEL. Given the varying quality and reliability of human data, it is also imperative to apply quality screening to select epidemiology studies of higher quality for exposure limit setting. When the human data are of lower quality or potentially ambiguous interpretation, the available animal toxicity data are considered. Working closely with exposure scientists to generate quality human evidence can also remove uncertainty and improve study reliability.

3.5 Pesticide exposure in fruit growing: comparison of levels measured under usual working conditions (CANEPA study) with those predicted by the registration process (EFSA model) for use in epidemiological studies

Morgane Bresson[1,2], Mathilde Bureau[3], Lucie De Graaf[3], Maylis Leblanc[3], Yannick Lecluse[1], Isabelle Baldi[3,4], Pierre Lebailly[1,2]

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Pesticide exposure increases the risk of chronic disease in farmers. Knowledge of exposure levels is needed for epidemiological and regulatory purposes. Since 2014, operator's and worker's exposure are assessed by EFSA respectively by AOEM and OPEX models, in pesticide registration process. However, data specific to fruit-growing farmers are very limited. We compared farmers' exposure in fruit growing, measured in field studies, with values predicted by registration.

We measured dermal exposure to the fungicides captan and dithianon in french farmers during 30 treatment and 121 re-entry (hail net folding and deployment, thinning, harvesting) days, with patches and cotton gloves, in 2016-2017. For 20 observations, exposure was recalculated from dislogeable foliar residues (DFR) measured several days after the last treatment. Detailed parameters (task, day, personal protective equipment (PPE) and treatment schedules) were used to calculate predicted values. Relationship between measured and calculated exposures was studied by linear regression.

For operators, overall, the model overestimated daily exposure and application exposure. Exposure at mixing/loading was underestimated in many observations, especially when the operator wore long working clothes or gloves. For workers, most exposures calculated using default settings were around 100 times higher than measured exposure. When we used measured DFR, exposure was underestimated by the model in all observations for dithianon and almost all for captan.

The models used for registration did not overestimate exposures in all circumstances, such as i) for mixing/loading where operators are exposed to concentrated products, and the protection provided by PPE appeared to be overestimated; ii) for re-entry when it does not occur immediately after spraying. Our results demonstrated the importance of using exposure studies under actual working conditions into the registration process in order to adopt a truly conservative approach.

3.8 Occupational exposure to pesticides and health outcomes: What is missing from epidemiological studies?

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Only a limited number of epidemiological studies evaluating a potential association between occupational exposure and health outcomes use exposure determinants explicitly designed to assess and predict potential pesticide exposure in agricultural workers. The absence of using exposure determinants specifically tailored to pesticide exposures may explain the lack of associations in epidemiological studies. We performed a meta-analysis following the PRISMA checklist to identify pesticide exposure determinants used in occupational studies. We included 71 of the 1436 studies identified and were able to successfully identify nine exposure determinants that most accurately characterized agricultural exposures to pesticides: active ingredients, chemical classes, types of PPP (plant protection products), crops, tasks, frequencies, duration, lifetime exposure days, and intensity-weighted exposure days. Seventeen studies showed statistically significant associations between exposure and health outcomes. Of these, only six studies were found with moderate quality of evidence (chemical class and cancer; crop types and cancer; life exposure days and cancer; intensity-weighted exposure days and cancer; duration and endocrine disruption; intensity-weighted exposure days and endocrine disruption). The strength of the association between exposures and health outcomes improved with increasing number of pesticide specific exposures determinants included in the study. We found a statistically significant association between cancer and the combination of the active ingredient and duration. Overall, relevant determinants to characterize PPP exposures for agricultural workers were not always included in the epidemiological studies. We recommend that a standardized list of PPP exposure determinants should be used in occupational exposure studies.

3.9 Bayesian benchmark dose modeling methods for epidemiological dose-response assessment using prospective cohort studies

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In the context of determining the toxicity value of chemicals for regulatory risk assessment, Benchmark dose (BMD) methodologies have traditionally been used with toxicological data. However, for epidemiological studies, which have diverse designs and data formats, there's a need for an evolved BMD approach. One methodology that stands out uses effective counts, such as the effective number of cases. This technique aims to represent data as if all groups were only varying in one factor, while being consistent in others – essentially providing a clearer view after adjusting for potential confounders. Stemming from recent research, our study zeroes in on prospective cohort studies, investigating different data types, specifically the "effective count"-based BMD. Our goal is to discern a more generalizable BMD framework for published cohort studies. Using a dataset that delves into the link between inorganic arsenic exposure and the onset of bladder and lung cancer, our analysis shows that modeling adjusted relative risk (RR) values as continuous data emerges as a more harmonized method. This aligns with established practices in BMD analysis using toxicological data. Furthermore, our exploration into Bayesian BMD methods indicates its potential in enhancing epidemiological risk assessment.

3.10 Operator's exposure to pesticide in non-agricultural areas: comparing field measurement of dermal contamination with registration predicted values

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Worker's exposure to glyphosate – the most sold herbicide worldwide – has been associated with increased risks of non-Hodgkin lymphoma and multiple myeloma. It has been estimated that 10% of its use concerns non-agricultural areas (NAA) such as greenspaces, public infrastructure and transportation networks but very few epidemiological and expology studies have included this sector.
In a non-controlled field study conducted in 2011 in France, actual dermal exposure of 23 operators who mix/load and apply glyphosate on NAA with knapsack sprayers was measured using the whole-body method. We compared these measured values with predicted levels given by OPEX, the model used for pesticide regulation in Europe since 2014. Each measured value had an estimated value and we tested their correlation using linear regression.
For body exposure, the model overestimated the exposure for all observations and there was no correlation between values. For hand exposure, however, estimated exposure was 42 times lower than measured exposure. Interestingly, when operators were wearing protective gloves, the model systematically underestimated the exposure, especially during the application (0.01 vs 0.93 mg/day). OPEX model succeed at overestimating body exposure but failed at being conservative regarding hand exposure, a major contributor of dermal exposure. It highly overestimated the protection afforded by the gloves.
At a time of glyphosate renewed approval in Europe, non-controlled field study conducted by academics are needed to improve OPEX prediction, especially in NAA, a sector not represented in the studies included in the model. Knapsack sprayers being the main equipment used worldwide in agriculture and NAA, it is also crucial to integrate new data specific to this equipment in the model. Operator's exposure should be estimated with accuracy in the registration process of pesticides to ensure proper safety as well as in epidemiological studies to improve exposure assessment.

3.11 Quantitative risk assessment for the introduction of Bluetongue virus into mainland Europe by long-distance wind dispersal of *Culicoides* spp.: a case study from Sardinia

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Europe faces regular introduction or re-introduction events of Bluetongue viral serotypes since the last 20 years, like the recent incursion of serotype 3 in Sardinia Island in 2018. While the long-distance wind dispersal of the disease vector, *Culicoides* spp., is recognized as a major disease introduction pathway, it remains poorly considered in risk assessments. A Quantitative Risk Assessment framework was developed to estimate the risk of Bluetongue virus (BTV) incursion into mainland Europe from Sardinia. Hysplit® model, an atmospheric dispersion tool, was used to infer the probability of airborne dispersion. Epidemiological disease parameters quantified the vector infection in Sardinia and its potential transmission in reached destinations. Two vector species (*C. imicola* and Obsoletus Complex), two host species (cattle and small ruminants), and spatiotemporal variations of environmental conditions were considered.
Risk of new BTV infection was mostly restricted to Sicily, south-western coast of Corsica and south-western part of Italy. Continental France (Mediterranean border), Balearic Islands (Spain) and the Italian peninsula were exposed sporadically to a risk only when considering at least 2 days of vector flight. No risk was evidenced above latitude 45°N. Highest risk periods for continental France were mid of June and end of October. The single contribution of *C.imicola* appeared insufficient to generate a risk of disease spread beyond Sardinia. Probability of aerial transport and vector-related parameters are the most influential variables in the model.
Our framework provides spatial and temporal risk insights to enhance preparedness against new introduction of Bluetongue disease.

3.12 Data analysis for risk categorization in relation to the implementation of biosecurity measures on pig farms in the period 2020-2022 and African swine fever outbreaks in 2022

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Introduction: In 2020 Food and veterinary Agency (FVA) launched -Animal Health Visits project which included Risk categorization in
relation to the implementation of biosecurity measures on pig farms. The purpose of this paper is to compare the data of the
categorized farms and the occurrence of ASF in relation to the previous categorization. The results of this research will provide a basis for improving the checklist, the scoring system and the methodology of the categorization in relation to implementation of biosecurity measures on pig farms.
Materials and Methods: In period from June 2020 to December 2022, 5608 pig farms were categorized by private veterinary
practitioners (PVPs) using FVA national score index system for biosecurity assessment. According to obtained scores, farms were classified into a low (up to 35 points), medium (36 to 55) and high (over 55) risk category. During the active and passive surveillance as well and in post outbreaks surveillance in 2022, a total of 5050 domestic pig were tested for ASF. Samples were taken from dead and suspicions animals. Also, sampling was carried out at the slaughterhouse for active surveillance as well for post outbreak surveillance
Results and Discussion: According FVA national score index system 708 pig farms were classified as farms with low biosecurity risk, 4219 with medium and 681 were categorized as farms with high biosecurity risk. The first ASF case in domestic pigs was confirmed on 7th January 2022 in two backyard farms. In total, 45 outbreaks were occurred until the end of 2022. The disease was detected in 15 pig farms, no previously registered and categorized, while 2 cases were confirmed as Illegal disposal of dead domestic pigs.
In categorized pig farms, ASF was diagnosed in 6 pig farms with high risk and in 14 pig farms with medium risk. However, unexpected ASF outbreaks were reported in 8 pig farms categorized with low biosecurity risk.
Conclusion: The results of this study indicate that there is a need for essential improvements in the methodology for risk categorization of pig farms. Biosecurity assessment should be based on higher and more rigorous criteria during farm evaluation and categorization.

3.13 Continued refinement of systematic review to better facilitate risk assessment needs – discussion of modifications to evidence synthesis and integration when considering observational data in dose-response assessment

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Risk analysts are often tasked with characterizing dose-response functions as part of risk assessments using evidence that clearly defines the specific dose of a substance relative to specific effects. Through the increased use of systematic review (SR), the inclusion and consideration of epidemiological data in the derivation of toxicological reference values (TRVs) have been elevated relative to historical practices. However, current SR guidelines are often arduous for practitioners to adhere to when these data are used in the development of TRVs. Most SR guidelines recommend using risk of bias (RoB) analyses to address the extent to which study results can accurately identify the relationship between exposure and outcome. Practitioners are increasingly finding that the concepts presented in the current SR guidelines do not sufficiently address the needs of risk assessors in determining whether studies meet the “relevance” and “reliability” categories for hazard or dose-response models. Additionally, while practitioners are aware that statistically significant results from observational studies are not sole evidence of a causal relationship, epidemiological studies are increasingly being used in the derivation of TRVs. Often there are significant uncertainties in exposure-response relationships due to residual bias, yet SR frameworks do not include steps or specific considerations for these uncertainties. As such, there is a need for the development and/or refinement of SR guidelines related to the use of observational data for use in dose-response modeling. Additional steps are needed to directly address “reliability” and “relevance” in the context of causality, and subsequently, appraisal as it relates to confidence in relying on such data for hazard and dose-response assessment. Such refinements would enhance the usefulness of the evidence integration step of current SR guidelines. This session will provide an overview of the general needs and concerns related to using epidemiological data for use in the derivation of TRVs and will discuss potential refinements to SR frameworks for evidence integration that includes “reliability” and “relevance” considerations for using epidemiological data in risk assessment. Comparisons will be made between the traditional criteria important to risk assessors related to selection of studies for dose response that robustly characterize exposure related effects relative to the lack of sufficient consideration for these same parameters in observational data. Examples of existing frameworks that compare and contrast these aspects will be included.

3.14 A survey of case studies in topic-specific and risk-specific refinement of risk of bias tools when considering observational studies in safety assessments

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While critical appraisal of risk of bias in systematic review is well-established, the use of risk of bias as a tool to assess the reliability and relevance of evidence used to support risk assessments is less well-established. The continued need for evolving and refining tools developed in evidence-based medicine for use in chemical risk assessment and food safety is highlighted by the variable use of risk of bias evaluation of observational epidemiological studies. Herein, we first provide a survey of risk of bias (or similar) approaches utilized by authoritative and regulatory entities in fields of toxicology and risk assessment, comparing and contrasting refinements that have been recognized important to risk assessment needs. Some entities, for example, have utilized risk of bias tools without refinement for risk assessment, whereas others have refined tools to include additional domains or elements to better characterize attributes important to risk assessment. Second, a series of case studies will be presented demonstrating the critical nature of refining risk of bias tools to both fit the needs of a research topic but also for risk assessment. These include case examples for assessing exposures to dioxins, PFAS compounds, caffeine, aspartame, and formaldehyde relative to specific outcomes including individual cancer types, reproductive effects (e.g., sperm count), cardiovascular effects, and various immune parameters. Collectively, these case studies demonstrate the importance of refining the risk of bias approach to better inform risk assessment decisions – and particular, in the characterization of uncertainty related to residual bias and the use or weight of observational studies for both hazard and dose-response assessment- and also demonstrate the need to consider aspects other than internal validity on an individual study basis in systematic reviews supporting risk assessments. Continued evolution of risk of bias is an important step to enhancing practitioner use of evidence-based tools in the conduct of safety assessments.

3.15 The impact of recall and selection bias on the association between talc and ovarian cancer in case-control studies

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Among observational epidemiology studies that have evaluated the association between perineal use of talc and ovarian cancer, case-control studies generally report small, positive associations, while the results of cohort studies are consistently null. We assessed how selection bias and recall bias may have contributed to positive associations in the case-control studies, and conducted a quantitative bias analysis to assess recall bias using publicly available data from the largest and most recent case-control study of talc and ovarian cancer as a case study. We found that assuming even a modest degree of recall bias led to attenuated odds ratios (ORs) for talc use and ovarian cancer, with 95% confidence intervals (CIs) that span the null. This was also the case when applying values based on self-reported talc exposure in the Sister Study, a prospective cohort study of environmental and genetic risk factors for breast cancer among sisters of women who have had breast cancer. We conclude that plausible amounts of bias can readily explain positive findings reported in this case study, and likely other talc case-control studies as well.

3.16 Conflict, consistency and emerging consensus: a critical interpretive synthesis to inform the evolution of systematic review guidance in environmental health

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Background: Systematic reviews are generally regarded as the most reliable and rigorous approach to evidence synthesis. Within the field of environmental health, systematic review methods are used to identify relationships between exposures, exposure mitigation interventions, and health outcomes. However, current frameworks inconsistently apply multiple strategies for conducting systematic reviews of exposures. This review aims to provide a comprehensive assessment of current systematic review frameworks, and to characterize similarities and differences between systematic review approaches from across the field of environmental health.

Methods: We performed an English-language search of MEDLINE via PubMed, EMBASE, and Cochrane databases from January 1, 2013 through March 30, 2023 for systematic review frameworks applied to environmental health research questions. Additionally, we searched 35 organizational websites and references of included studies to identify additional frameworks outside of the peer-reviewed literature. For the critical interpretive synthesis, we purposively sampled and extracted data from frameworks that contributed new information to at least one of the following themes grounded in the PRISMA framework: research question, protocol, search strategy, study selection, data extraction, data synthesis, risk of bias assessment, overall certainty assessment, reporting findings, disclosure of funding and conflict of interest, feasibility considerations, limitations, and future research.

Results: From 3,417 studies identified through the database search, we included 5 published frameworks. We included another 16 frameworks identified from organizational websites and citation searching; 14 frameworks were included in our purposive sample. Most frameworks (n = 10) originated from North America. Five frameworks addressed all of our predefined themes; all frameworks addressed at least 6 of the 9 themes. Additionally, 9 frameworks described an approach to integrating epidemiologic data with information from animal or in vitro studies. Although we observed variability in whether or how thoroughly frameworks addressed each of the themes, different approaches did not contradict each other within a theme. Rather, frameworks differed in the degree of methodological rigor that was suggested or recommended.

Discussion: This systematic review and critical interpretive synthesis provides a comprehensive overview of systematic review approaches in environmental health, proposing necessary domains to guide systematic reviews in environmental health. Operational guidance complements the proposed framework domains. Findings may be useful to researchers who are selecting an approach for their review, or developing resources to facilitate the uptake of systematic methods for reviews of environmental exposures.

3.17 The environmental burden of disease method applied in a comparative risk assessment for children and adolescents in Germany – experiences from the UKAGEP project

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Introduction: The environmental burden of disease (EBD) method is a specific application of the comparative risk assessment methodology and allows to quantify summary measures of population health. Within the UKAGEP project (Environmental Burden of Disease and Health Parameters) we applied this method in order to quantify the burden attributable to selected environmental risk factors for children aged 3 to 17 years in Germany.

Method: We used the EBD method, developed by the World Health Organization, to calculate disability-adjusted life years (DALYs) and other measures of disease burden. Systematic literature searches were conducted to identify exposure-response functions from epidemiological studies. Suitable exposure and health data were obtained from the fifth population-representative German Environmental Health Survey (GerES V, 2014-2017) and additional data sources.

Results: EBD calculations were performed for 5 of the 18 previously selected risk factors: Secondhand smoke, bisphenol A, traffic noise, benzene, and particulate matter (PM2.5). For example, about 7,800 (confidence interval: 5,200-10,400) DALYs due to atopic dermatitis, hay fever, asthma, otitis media, lower respiratory tract infection, and sudden infant death can be attributed to second hand smoke and nearly 5 % (1,300, confidence interval: 800-2,000) of the DALYS for lower respiratory tract infections in 3-17-year-olds were attributable to PM2.5 in 2016.
The two main limiting factors were the lack of suitable exposure-response functions for children and adolescents and their low exposures identified in GerES V. This does not mean, that the concentrations determined were generally uncritical in terms of possible health effects. However, the levels were not associated with any burden in the EBD framework.

Conclusions: The EBD method requires a number of input data that are not readily available for children and adolescents in Germany. This limits a comprehensive overview of their EBD even if exposure data are obtained in a cross-sectional study like GerES V.

3.18 Triangulated phylodynamic-spatio-temporal analysis of A/H5N1 outbreak in cats in Poland during spring/summer 2023

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Background :
One Health topics such as transmission of zoonotic agents of domestic/wild birds and environmental residue problems, food and feed safety become increasingly important to modern society in the post pandemic times. We performed phylodynamic-spatio-temporal analysis of A/H5N1 epizootic in cats in Poland in Spring-Summer 2023.

Data & Methods :
Data and methods triangulation were applied based on: 1) 30 (positive) and 27 (negative) cases from WOAH reference lab, 2) suspected 87 cases submitted by animal owners (participatory epidemiology), 3) daily time series of i) Google queries for Avian Influenza (AI), cats disease and cats deaths, as well as ii) mentions of cat/cats and AI in social and traditional media. 4) 19 RNA sentences of viruses.
Wildbirds abundance and distance to water reservoirs and trajectories of birds' migratory paths were used as covariates. We compared the chain and hierarchical structure of clusters of various types of data in multidimensional space.

Results :
1.Positive cases form chains structure both on bird migration paths and close to high abundance of nesting sites of waterbirds (verified by comparison of Average Nearest Neighbour distance and betweenness clustering of positive case vs both controls);2.The A/H5N1 was already probably circulating in cats in the second half of May in regions bordering with Ukraine (a month before first confirmed case);3.There are at least 2 (eastern and western Poland) separate introductions of viruses (according to k-mean and DBScan).

Conclusions :
We recommend active monitoring (serology) of water birds (these overwintering for some reasons), rodents and cats in Pomerania and selected sites in Western Poland (as maybe some low viral pressure were still there the latest in July). Common outbreak investigation of veterinary and sanitary inspection revealed multiple gaps in emerging new zoonotic threats. Thus, use of unconventional data and infodemic management should be incorporated into surveillance/risk assessment schema, because we might handle similar problems in the next few years in Europe.

4 List of authors