Critical review of the EFSA approach

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Man's mind cannot grasp the causes of events in their completeness, but the desire to find those causes is implanted in man's soul. And without considering the multiplicity and complexity of the conditions any one of which taken separately may seem to be the cause, he snatches at the first approximation to a cause that seems to him intelligible and says: "This is the cause!"

Leo Tolstoy
War and Peace; Book Thirteen: 1812; Chapter 1

Main messages

- We have a problem with health risk assessment of pesticides (not only pesticides; not only epidemiology)
- The most complex issue in epidemiological studies of pesticides is exposure assessment. There are solutions to this
- “Exposome” approaches open new possibilities for research and advanced risk assessment bridging toxicology and epidemiology
- We need more funding on pesticides research
- The EFSA Scientific Opinion could be significantly improved
- EFSA needs to standardize protocols

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Pesticides and cancer

Lindane, classified as human carcinogen (Group 1) in relation to risk of non-Hodgkin Lymphoma (*IARC 2015; D Loomis, Lancet Oncol, 2015*)

Why is there only one insecticide classified as human carcinogen by IARC/WHO?

Lack of convincing evidence for other pesticides clearly shows the difficulties in evaluating the carcinogenicity of many chemical agents in human populations

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Oncol, 2015)

Why is there
by IARC/WHO

Lack of convi
difficulties in
agents in hum

- standard environmental toxicity tests used to license pesticides are performed on particular test species and have limited predictive power when chemicals are used widely *(see also Milner and Boyd, Science 2017)*

- low level of trust in current toxicology testing regimes because of serious difficulties to encompass the full range of toxic effects that could emerge when a pesticides is used at scale

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Main messages

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Nature of exposures in agriculture

- Seasonal
- Often outdoors but also indoors
- Highly variable
  - Type of agent and exposure
  - Biological, chemical and physical
  - Individual agents (active ingredients; adjuvants)
  - Intensity, duration and frequency
- Multiple agents
- Multiple routes
- Not limited to farmers

(slide modified from Hans Kromhout, Univ Utrecht)

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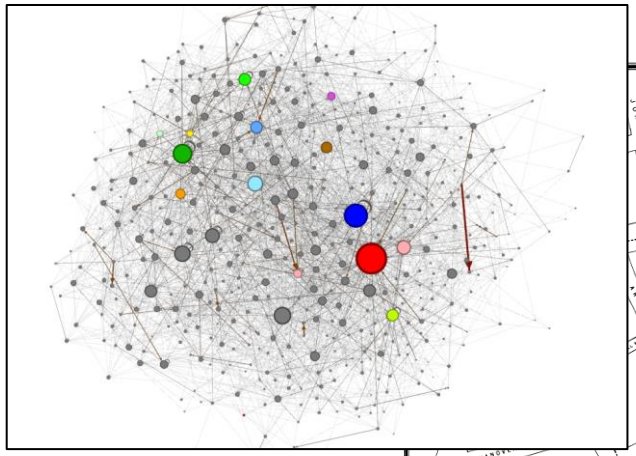
The Exposome

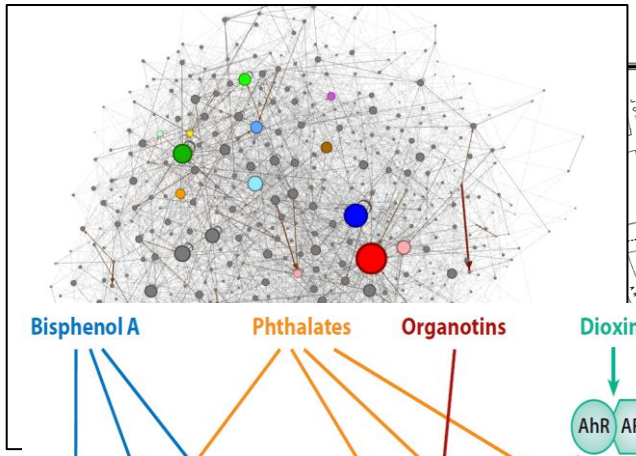
Recognizing the disparity in current knowledge between genes and environmental exposures, Chris Wild (2005) defined the "exposome" representing *all environmental exposures (including those from diet, lifestyle, and endogenous sources) from conception onwards,* as a quantity of critical interest to disease etiology.

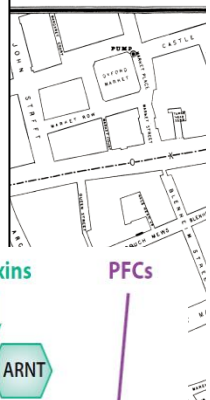
“Modern” Epidemiology

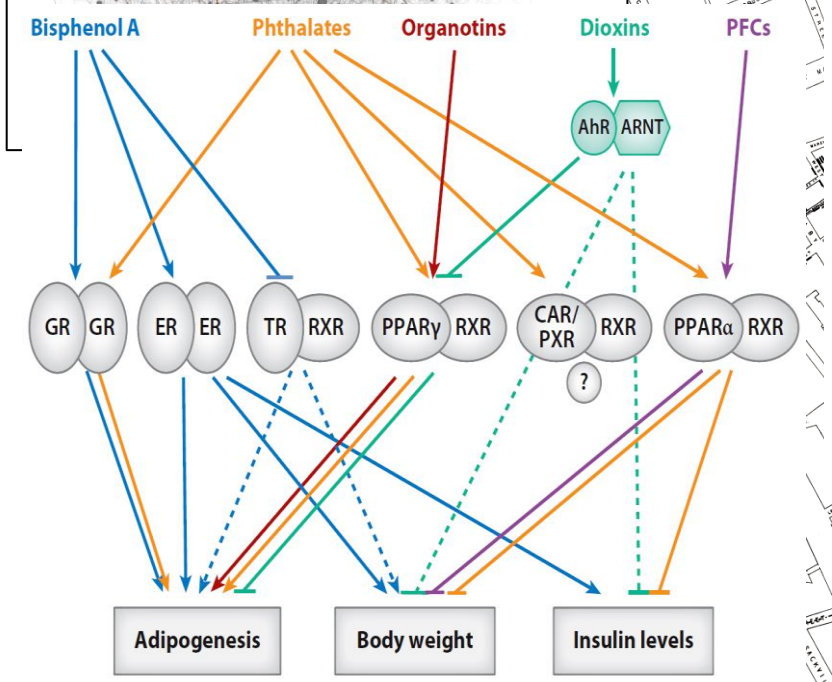


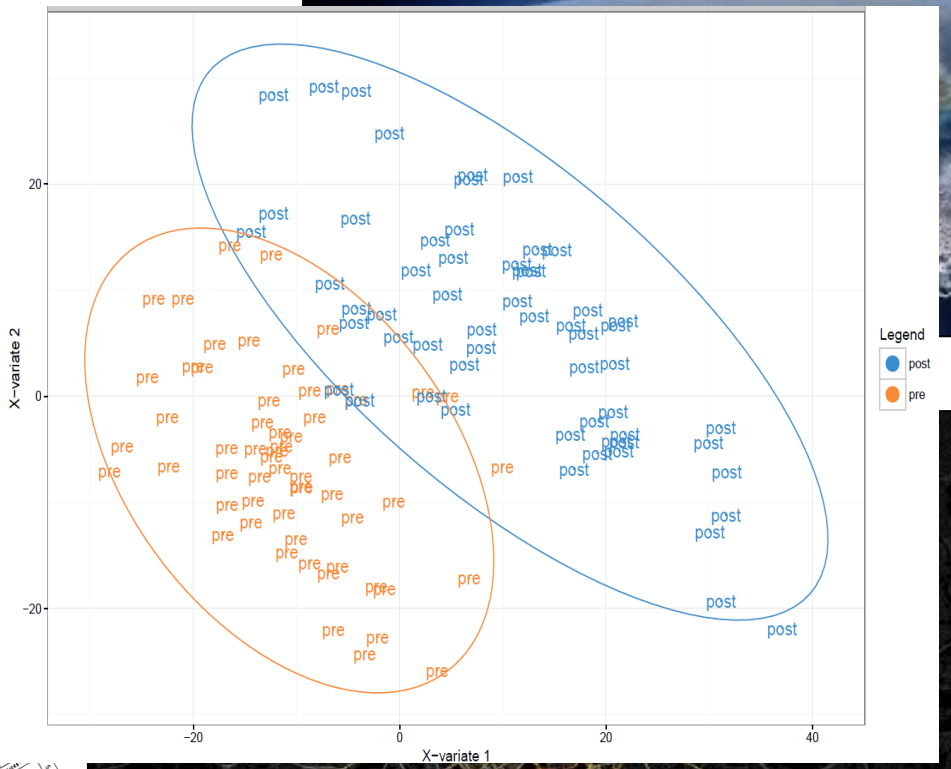
(Slide from Perry Hystad, Oregon State University)

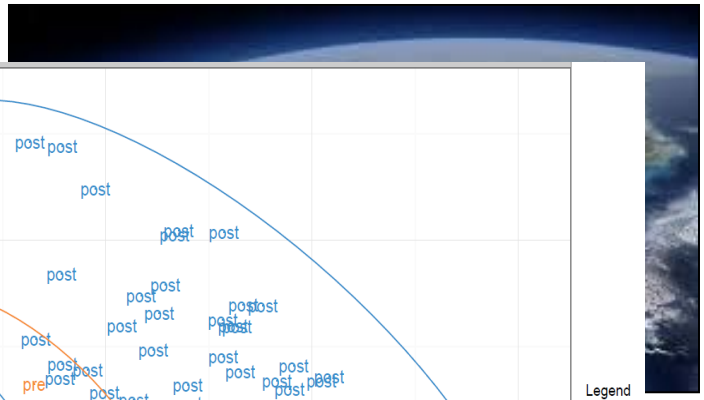
“Modern” Epidemiology

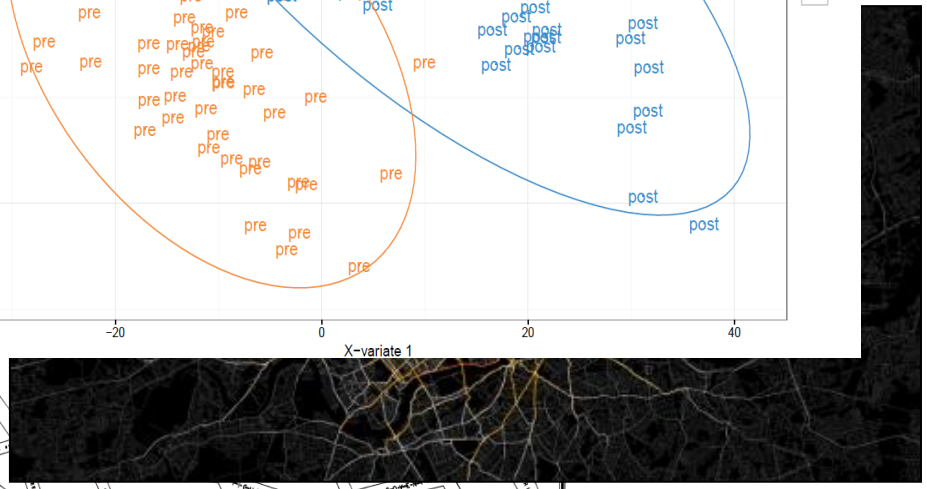


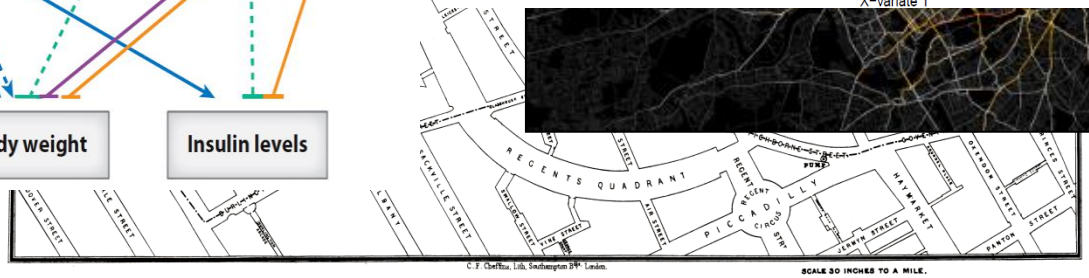












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Serious underfunding of research on pesticides

- Most of the evidence in human from studies examining mainly other risk factors (hence no detailed analysis of pesticides- hence not surprising that these data cannot be used in risk assessment)
- Some major studies funded (a mistake to consider only AgHealth)
- We need 100M€ (indicative amount) to do a couple of new powerful cohort studies in different settings. Multidisciplinary, extensive industrial hygiene, repeated biomarkers, omics, long term follow-up

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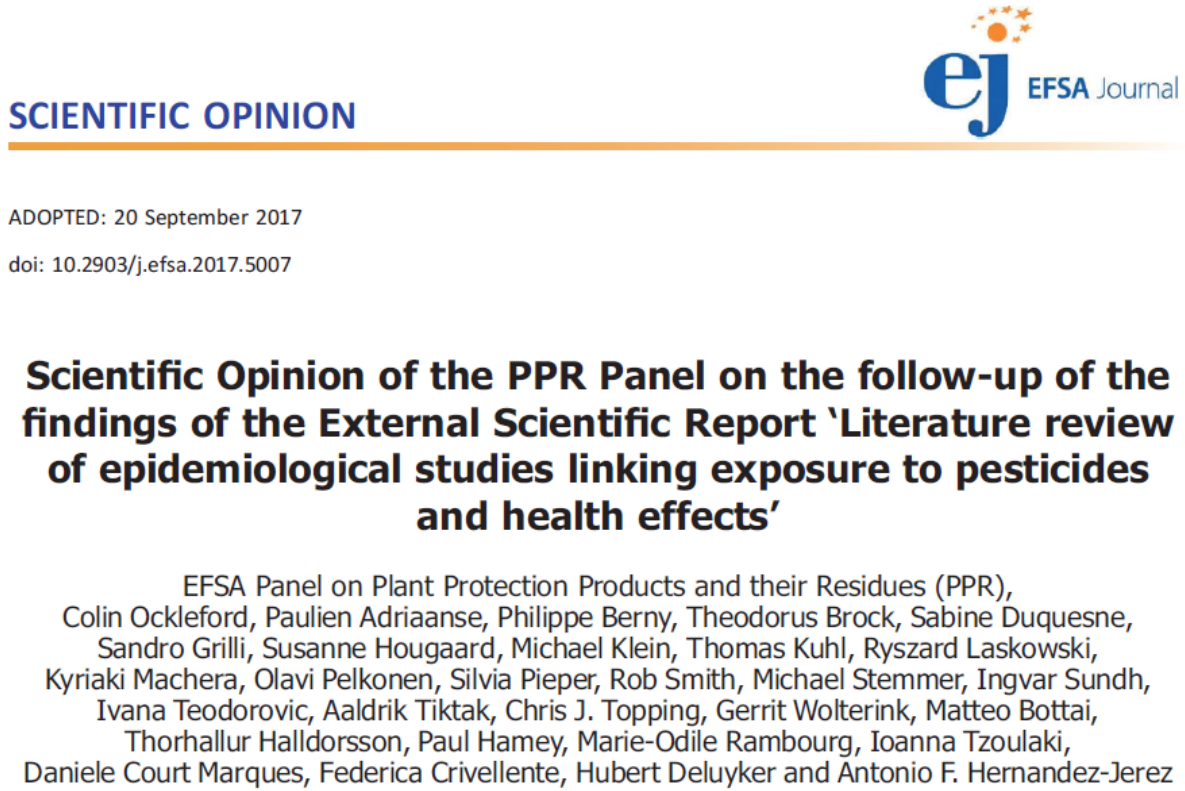
The EFSA Scientific Opinion: a report on epidemiology written by non-epidemiologists. An interesting endeavour (for the authors) but not an EFSA document



SCIENTIFIC OPINION

EFSA Journal

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Scientific Opinion of the PPR Panel on the follow-up of the findings of the External Scientific Report 'Literature review of epidemiological studies linking exposure to pesticides and health effects'

EFSA Panel on Plant Protection Products and their Residues (PPR),
Colin Ockleford, Paulien Adriaanse, Philippe Berny, Theodorus Brock, Sabine Duquesne, Sandro Grilli, Susanne Hougaard, Michael Klein, Thomas Kuhl, Ryszard Laskowski, Kyriaki Machera, Olavi Pelkonen, Silvia Pieper, Rob Smith, Michael Stemmer, Ingvar Sundh, Ivana Teodorovic, Aaldrik Tiktak, Chris J. Topping, Gerrit Wolterink, Matteo Bottai, Thorhallur Halldorsson, Paul Hamey, Marie-Odile Rambourg, Ioanna Tzoulaki, Daniele Court Marques, Federica Crivellente, Hubert Deluyker and Antonio F. Hernandez-Jerez

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The EFSA Scientific Opinion: comments submitted by ISEE

- **Epistemological** (toxicologic studies versus epidemiology)
- **Mechanistic** (favor ranking etc., rather than a integrated assessment of knowledge)
- **Missing considerations** (no advocacy for the necessary substantial ongoing stream of funding for surveillance and post-marketing surveillance of pesticides that could strengthen our capacity to identify real life events, nor for expanded, diversified, well-funded, and more detailed epidemiologic studies being now concentrated in just some centers and labs)
- **Vulnerability of study populations** (strengths of epidemiology to examine real life conditions of exposure and disease, vulnerable populations, and real life outcomes that can happen and are seldom observed in vivo)

The EFSA Scientific Opinion: comments by ISEE

- Writing: unequal; many parts valuable; overall could be improved
- Overall message of the report: epidemiology is not reliable, text making systematically broad generalizations
    - Many cliché on causal inference, ranking of evidence etc
    - Important areas poorly covered, e.g. retrospective exposure assessment and biomonitoring, post market surveillance
- Scope: unclear (or at least poorly described)

Occupational Human carcinogens (Group 1- IARC)

- **118** agents in Group 1
- **57** are occupational or also occur in the occupational environment (e.g. aflatoxins, SHS, radiations etc)
- Of those, **36** were identified as Group 1 before the year 2000, and **21** after the year 2000

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Probable Occupational Human carcinogens (Group 2A- IARC)

- **81** agents in Group 2A (probable carcinogens)
- **48** are occupational
- Of those, **20** were identified as Group 2A before the year 2000, and **28** after the year 2000
- Use of evidence on mechanisms very important for this group (upgrade from 2B-possible to 2A-probable)

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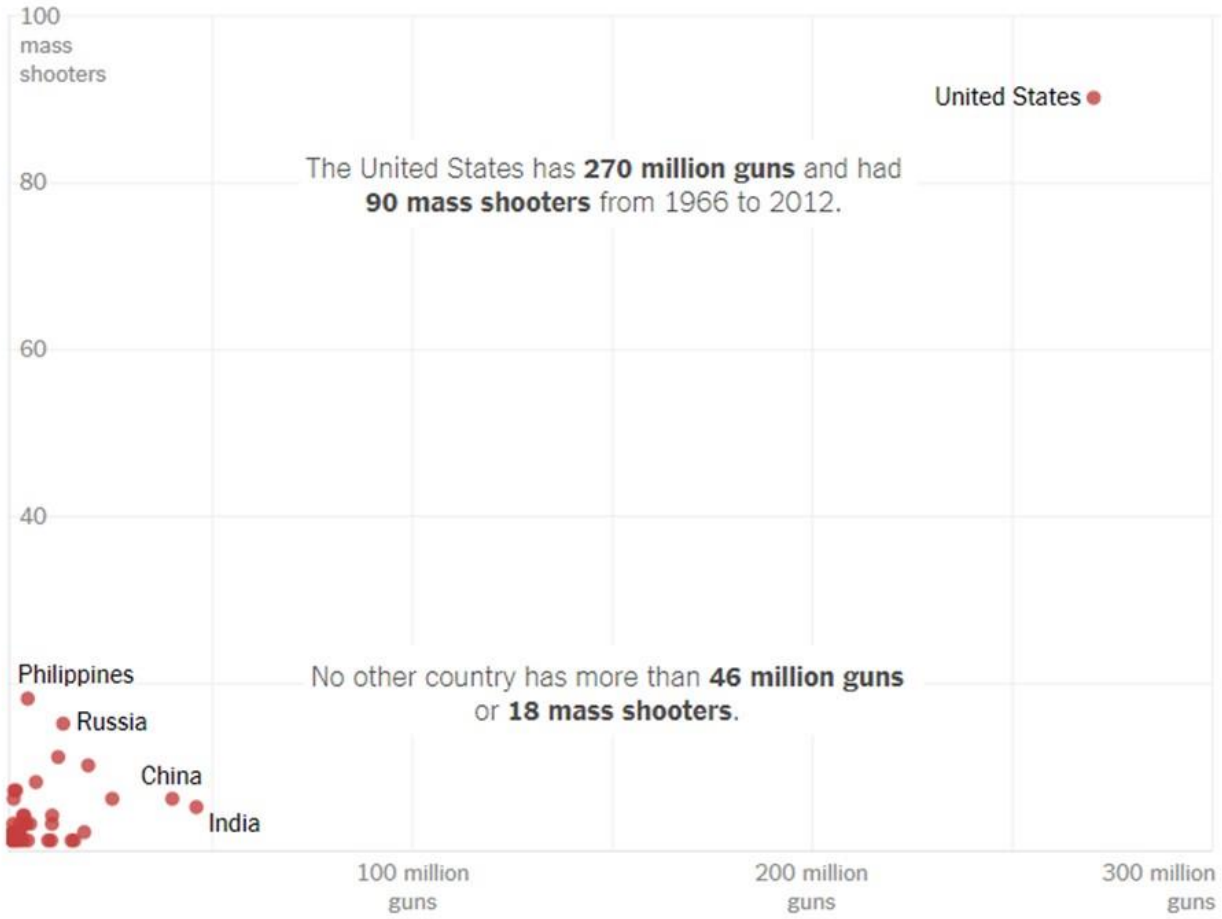
There is no predefined hierarchy in study design.

RCTs are good for clinical settings and not good for environmental, occupational and many other exposures



The EFSA Scientific Opinion: out of scope

Conclusions of the report (p58):

'The PPR Panel will specifically':

1) Collect and review all sources of gaps and limitations … , of the available epidemiological studies.

2) Based on the gaps and limitations identified in point 1, propose potential refinements for future epidemiological studies to increase the quality, relevance and reliability … This may include study design, exposure assessment…

3) Identify areas in which information and/or criteria are insufficient or lacking and propose recommendations for how to conduct pesticide epidemiological studies in order to improve and optimise the application in risk assessment. …

4) Discuss how to make appropriate use of epidemiological findings in risk assessment of pesticides during the peer review process of draft assessment reports, e.g. WoE as well as integrating the epidemiological information with data from experimental toxicology, AOPs, mechanism of actions, etc.

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ISEE's comments to draft

- We suggest a balanced panel, addressing the overall production of pesticide science, aiming to enhance the integration and advancement of knowledge.
- We urge EFSA to develop and apply standardized protocols for risk assessment rather than ask each panel to improvise and produce position papers on issues that are not within their area of knowledge as is the case with the pesticides paper.

ISEE's comments to draft

- We urge EFSA to consider in developing these protocols relevant guidelines for systematic review of evidence that already exist e.g. in WHO.
- We urge EFSA to consider that older reports such as the WHO "guidelines for guidelines" have been modified to enable the application of a wider more holistic perspective concerning the types of evidence to be used

The role of epidemiology

- Science is one and epidemiology works integrated with other sciences;
- Epidemiology as any other science is advancing, and to further contribute to the assessment of the health effects of pesticides requires of independent and rigorous research well-funded, as well as the input from post marketing surveillance;
- We have to take advantage of our understanding of the "exposome" and need to consider it on the real vulnerabilities of population, only provided through population (epidemiologic) research.

New approaches for risk assessment

- Transformational change in the breadth and depth of exposure assessment that would improve integration with and responsiveness to toxicology and epidemiology
- Questions as to whether or how the data now being generated can be used to improve risk-based decision-making
- We need to invest in common understanding and exchange of ideas and link modern exposure assessment, molecular epidemiology/exposome with toxicological approaches on mode of Action/Adverse Outcome Pathways. Both are in combination essential to establish evidence based risk assessments and policies

thank you, on behalf of the

International Society for Environmental Epidemiology (ISEE) and EPICOH

Acknowledgments

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ISEE Policy Committee: Michal Krzyzanowski, Chair, Carlos Santos Burgoa, Tony Fletcher, Silvia Medina, Erik Lebret

EPICOH: Roel Vermeulen, Chair; Aaron Blair, Hans Kromhout

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ISEE would be happy to propose joint concrete initiatives to identify knowledge gaps, establish procedures and review processes and to outline a research agenda on epidemiology studies of health effects of pesticides