Environ Health Perspect

DOI: 10.1289/EHP3067

Supplemental Material

Weight of Evidence for Hazard Identification: A Critical Review of the Literature

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Table S1. National and international agencies or organizations performing risk assessment that were consulted for guidance as part of the current study

Agency or organization	*Location*
IARC (International Agency for Research on Cancer) - Monographs program	International
FAO (Food and Agriculture Organization of the United Nations) - JEMRA (Joint FAO/WHO Expert Meetings on Microbiological Risk Assessment) - JECFA (Joint FAO/WHO Expert Committee on Food Additives)	International
OECD (Organization for Economic Co-operation and Development)	International
WHO (Word Health Organization)	International
ECETOC (European Centre for Ecotoxicology and Toxicology Of Chemicals)	European
WCRF/AICR (World Cancer Research Fund International / American Institute for Cancer Research)	International
ECHA (European Chemicals Agency)	European agency
EFSA (European Food Safety Authority)	European agency
EMA (European Medicines Agency)	European agency
JRC (Joint Research Center)	European Commission
SCCS (Scientific Committee on Consumer Safety)	European Commission
SCHER (Scientific Committee on Health and Environmental Risks)	European Commission
SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks)	European Commission
BfR (German Federal Institute for Risk Assessment)	Germany
UBA (German Federal Environmental Agency)	Germany
UFZ (Helmholtz Centre for Environmental Research)	Germany
AGES (Austrian Agency for Health and Food Safety)	Austria
AFSCA (Belgian Federal Agency for the Safety of the Food Chain)	Belgium
Risk Assessment Center (RAC) - Bulgarian Food Safety Agency	Bulgaria
SGL (State General Laboratory)	Cyprus
Croatian Food Agency	Croatia
DTU-Food (National Food Institute DTU)	Denmark
AECOSAN (The Spanish Agency for Consumer Affairs, Food Safety and Nutrition)	Spain
Ministry of Agriculture of Estonia - Food Safety Department	Estonia
Evira (Finnish Food Safety Authority)	Finland
EFET (Hellenic Food Authority)	Greece
National Food Chain Safety Office	Hungary
The Icelandic Food and Veterinary Authority	Iceland
FSAI (Food Safety Authority of Ireland)	Ireland
Istituto Superiore di Sanità (ISS)	Italy
Institute of Food Safety, Animal Health and Environment “BIOR”	Latvia
National Food and Veterinary Risk Assessment Institute	Lithuania
Ministry of Agriculture, Ministry of Health	Luxembourg
Malta Competition and Consumer Affairs Authority	Malta
FHI (The Norwegian Institute of Public Health)	Norway
VKM (The Norwegian Scientific Committee for Food Safety)	Norway
NVWA (Food and Consumer Product Safety Authority)	Netherlands
PBL (Netherlands Environmental Assessment Agency)	Netherlands
RIVM (National Institute of Public Health and the Environment) RIVM/MNP (Netherlands Environmental Assessment Agency)	Netherlands
IRAS (University of Utrecht · Institute for Risk Assessment Sciences)	Netherlands
ASAE (Portuguese Economy and Food Safety Authority)	Portugal
Ministry of Agriculture and Rural Development of the Slovak Republic	Slovak Republic
Ministry of Agriculture of the Czech Republic	Czech Republic
Polish EFSA Focal Point	Poland

National Sanitary Veterinary and Food Safety Authority	Romania
FERA (Food and Environment Research Agency)	United Kingdom
FSA (UK Food Standards Agency)	United Kingdom
Centre for Mathematical Sciences (Cambridge)	United Kingdom
Imperial College London	United Kingdom
MRC (Medical Research Council)	United Kingdom
University of Durham	United Kingdom
Ministry of Agriculture Forestry and Food	Slovenia
SLV (National Food Agency)	Sweden
FSVO (Federal Food Safety and Veterinary Office)	Switzerland
ETH Zurich (Swiss Federal Institute of Technology in Zurich)	Switzerland
INSPQ (Institut national de santé publique du Québec)	Canada
Health Canada	Canada
ATSDR (Agency for Toxic Substances and Disease Registry)	USA
US FDA (US Food and Drug Administration)	USA
NIOSH (CDC-National Institute for Occupational Safety and Health)	USA
NIEHS (NIH - National Institute of Environmental Health Sciences)	USA
US NRC (United States Nuclear Regulatory Commission)	USA
NZFSA (New Zealand Food Safety Authority)	New Zealand

Table S2. Definitions of weight of evidence and line of evidence identified in the literature

Reference	Definition	Interpretation
Rhomberg et al. (2013)	"When we refer to WOE frameworks, we mean approaches that have been developed for taking the process all the way from scoping of the assessment and initial identification of relevant studies through the drawing of appropriate conclusions."	Transparent framework for drawing conclusions
Krimsky et al. (2005)	"Walker (1996) cites three objectives of a WOE analysis: (1) it provides a clear and transparent framework for evaluating the evidence in a risk determination; (2) it offers regulatory agencies a consistent and standardized approach to evaluating toxic substances; (3) it helps to identify the discretionary assumptions in risk determinations from experts."	
USEPA (2005; 2011)	EPA often uses the term in the context of a WOE "narrative." In the case of a carcinogenic risk assessment, the narrative consists of a short summary that "explains what is known about an agent's human carcinogenic potential and the conditions that characterize its expression" (USEPA 2011). In EPA's Guidelines for Carcinogen Risk Assessment, the WOE narrative "explains the kinds of evidence available and how they fit together in drawing conclusions, and it points out significant issues/strengths/limitations of the data and conclusions" (USEPA 2005, p. 1-12).	
Krimsky et al. (2005)	"A process or method in which all scientific evidence that is relevant to the status of a causal hypothesis is taken into account."	
Hope and Clarkson (2014)	"The process of considering the strengths and weaknesses of various pieces of information in order to inform a decision being made among competing alternatives"	Process of considering the strengths and weaknesses of various pieces of information
USEPA (2014)	"The present committee found that the phrase weight of evidence has become far too vague as used in practice today and thus is of little scientific use. In some accounts, it is characterized as an oversimplified balance scale on which evidence supporting hazard is placed on one side and evidence-refuting hazard on the other. That analogy neglects to account for the total weight on either side (that is the scope of evidence available) or captures only where the balance stands. Others characterize WOE as a single scale, and different kinds of evidence have different weights. For example, a single human study with low risk of bias might be considered as providing the same evidential weight as three well-conducted animal studies. The weights might be adjusted according to the quality of the study design. This analogy neglects to account for the weight for vs the weight against hazard. Perhaps the overall idea of the WOE for hazard should combine both characterizations. It is evident, however, that its use in the literature and by scientific agencies, including EPA, is vague and varied."	
Krimsky et al. (2005)	"Includes all varieties of evidence, positive and negative, mechanistic and non-mechanistic, in vivo and in vitro, as well as human and animal studies."	Integration of different lines of evidence
Alexander et al. (2012)	"Several well-established methods of evidence-based research synthesis: the hierarchy of research study designs, the systematic narrative review, meta-analysis, and application of so-called causal criteria. Our approach to WOE included the idea that all (rather than some) of the evidence would be considered, emphasizing (i.e., putting more weight) studies that tested the scientific hypotheses better than others."	
Linkov et al. (2009)	"Weight of evidence (WOE) can be defined as a framework for synthesizing individual lines of evidence, using methods that are either qualitative (examining distinguishing attributes) or quantitative (measuring aspects in terms of magnitude) to develop conclusions regarding questions concerned with the degree of impairment or risk. In general, qualitative methods include presentation of individual lines of evidence without an attempt at integration, or integration through a standardized evaluation of individual lines of evidence based on qualitative considerations. Quantitative methods include integration of multiple lines of evidence using weighting, ranking, or indexing as well as structured decision or statistical models."	
Goodman et al. (2010)	WOE = "a methodology with a simple premise: that all available evidence should be examined and interpreted (Weed 2005)".	
Khosroyan et al. (2015)	Integration of different lines of evidence (chemical concentrations, toxicological responses, in situ surveys) lies at the basis of the WOE approach	
Piva et al. (2011)	"the concept of weight of evidence (WOE) integrates data from different studies, or lines of evidence (LOEs), that address questions relating to the presence of chemical pollutants, their bioavailability, and the onset of adverse effects at	

	different levels of biological organization, i.e. from a molecular level to organism or community effects (Chapman and Hollert, 2006)"	
Marvier (2011)	"Sometimes the phrase weight of evidence is invoked when a reviewer has simply drawn her or his own conclusions about a series of studies without any formal analytical tools, whereas on other occasions weight of evidence is used to describe a rigorous quantitative synthesis of effect size from multiple experiments."	
Hope and Clarkson (2014)	"In short, a WOE approach is a synthetic process that combines the information content of multiple weighted pieces of evidence (Suter and Cormier 2011)".	
Gosling et al. (2013)	"WOE consists in combining lines of evidence of varying quality in a risk assessment"	No interpretation
Linkov et al. (2011)	"WOE consists of a diverse set of methods, often built for particular applications"	
Hristozov et al. (2014a)	"Set of information used to evaluate endpoint. Lines of evidence are not all equally important in making the overall conclusion"	
Hope and Clarkson (2014)	"Line of evidence is a measure associated with a specific risk hypothesis. Multiple lines of evidence can be associated with a single risk hypothesis"	

Note: USEPA, U.S. Environmental Protection Agency

Figure S1. Template to summarize WOE information from Source Documents

	Description of the document				
1	Document ID		2	Name of the reviewer	
3	Year of publication		4	Type of document	
5	# pages of interest				
6	Authors/Institution (country)				
7	Title				
8	Document Status				
9	Document selected for further consideration: Yes - No				

10	Domain covered	
	Occupational health: Yes - No	Environmental Health: Yes - No
	Microbiology (food): Yes - No	Chemistry (food): Yes - No
	Animal health: Yes - No	Nutrition: Yes - No
	Plant health: Yes - No	Other:

11	Study type
	Assessment of individual study: Yes - No
	Assessment of synthesis of studies or lines of evidence: Yes - No

	Elements of WOE described in the document	
11	Definition of Weight of Evidence:	
12	Approaches developed or recommended (Names and references):	
14	Types of studies considered - Comments/Description of considerations in assessing/weighting	
	In vivo experimental study: Yes - No In vitro experimental study: Yes - No Human intervention study: Yes - No Epidemiological study: Yes - No Other: Yes - No	
15	Relevant case studies	
16	Limitations of application of the approach/recommendations	
17	WOE ranking	
18	Criteria for levels of evidence:	

19	Additional information (WOE communication, WOE process, etc.):

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