

REVIEW ARTICLE

## Illustrative case using the RISK21 roadmap and matrix: prioritization for evaluation of chemicals found in drinking water

Douglas C. Wolf<sup>1</sup>, Ammie Bachman<sup>2</sup>, Gordon Barrett<sup>3</sup>, Cheryl Bellin<sup>4</sup>, Jay I. Goodman<sup>5</sup>, Elke Jensen<sup>6</sup>, Angelo Moretto<sup>6</sup>, Tami McMullin<sup>7</sup>, Timothy P. Pastoor<sup>1</sup>, Rita Schoeny<sup>8</sup>, Brian Slezak<sup>4</sup>, Korinna Wend<sup>9,10</sup> & Michelle R. Embry<sup>11</sup>

<sup>1</sup>Syngenta Crop Protection LLC, Greensboro, NC, USA, <sup>2</sup>ExxonMobil Biomedical Sciences, Inc., Annandale, NJ, USA, <sup>3</sup>Health Canada, Ottawa, Ontario, Canada, <sup>4</sup>DuPont Haskell Global Centers for Health & Environmental Sciences, Newark, DE, USA, <sup>5</sup>Pharmacology & Toxicology, Michigan State University, East Lansing, MI, USA, <sup>6</sup>Department of Biomedical & Clinical Sciences, University of Milan, Milan, Italy, <sup>7</sup>Dow Corning Corporation, Midland, MI, USA, <sup>8</sup>United States Environmental Protection Agency, Washington, DC, USA, <sup>9</sup>Department of Orthopaedic Surgery, UCLA and Orthopaedic Hospital, Los Angeles, CA, USA, <sup>10</sup>Orthopaedic Hospital Research Center, David Geffen School of Medicine at UCLA, Los Angeles, CA, USA, and <sup>11</sup>ILSI Health and Environmental Sciences Institute, Washington, DC, USA

### ABSTRACT

The HESI-led RISK21 effort has developed a framework supporting the use of twenty-first century technology in obtaining and using information for chemical risk assessment. This framework represents a problem formulation-based, exposure-driven, tiered data acquisition approach that leads to an informed decision on human health safety to be made when sufficient evidence is available. It provides a transparent and consistent approach to evaluate information in order to maximize the ability of assessments to inform decisions and to optimize the use of resources. To demonstrate the application of the framework's roadmap and matrix, this case study evaluates a large number of chemicals that could be present in drinking water. The focus is to prioritize which of these should be considered for human health risk as individual contaminants. The example evaluates 20 potential drinking water contaminants, using the tiered RISK21 approach in combination with graphical representation of information at each step, using the RISK21 matrix. Utilizing the framework, 11 of the 20 chemicals were assigned low priority based on available exposure data alone, which demonstrated that exposure was extremely low. The remaining nine chemicals were further evaluated, using refined estimates of toxicity based on readily available data, with three deemed high priority for further evaluation. In the present case study, it was determined that the greatest value of additional information would be from improved exposure models and not from additional hazard characterization.

**Abbreviations:** ADI: Acceptable Daily Intake; ATSDR: US Agency for Toxic Substances and Disease Research; EFSA: European Food Safety Authority; ECHA: European Chemicals Agency; FAO: Food and Agriculture Organization; HESI: Health and Environmental Sciences Institute; ILSI: International Life Sciences Institute; IRIS: US EPA Integrated Risk Information System; JMPR: Joint Meeting on Pesticide Residues; MOE: Margin of Exposure; NAS: US National Academy of Sciences; NOEL: No observable effect level; NTP: US National Toxicology Program; OECD: Organization for Economic Cooperation and Development; PMRA: Pest Management Regulatory Agency; RfD: Reference Dose; RISK21: Risk Assessment in the 21st Century; TTC: Threshold of toxicological concern; USEPA: United States Environmental Protection Agency; WHO: World Health Organization

### ARTICLE HISTORY

Received 10 April 2015  
Revised 8 July 2015  
Accepted 11 August 2015

### KEYWORDS

Drinking water, integrated evaluation strategy, prioritization, risk assessment, RISK21, tiered approach

### Table of contents

Introduction	44	Estimation of toxicity	49
Case study overview	44	Conclusions from second evaluation	49
Problem formulation	46	Third evaluation	49
First evaluation	46	Estimation of exposure	49
Estimation of exposure	46	Estimation of toxicity	49
Estimation of toxicity	47	Information gathering	49
Conclusions from first evaluation	48	Use of the matrix	49
Second evaluation	48	Prioritization decision	50
Estimation of exposure	48	General conclusions	52
		Acknowledgements	52

Declaration of interest	52
References	52

## Introduction

The ILSI Health and Environmental Sciences Institute (HESI) created the Risk Assessment in the 21<sup>st</sup> Century (RISK21) Project to address issues and catalyze improvements in human health risk assessment in the light of recent reports by the US National Academy of Sciences (NAS), the Canadian Academies and the European Union. These reports have called for changes in exposure assessment, toxicity testing and human health risk assessment (Council of Canadian Academies 2012; European Commission 2012; National Research Council 2007, 2008, 2009, 2012). The overall goal of RISK21 was to develop a framework that enhanced the way by which information for chemical risk assessment is obtained, evaluated and used. The RISK21 project, which began in 2009, involved over 120 individuals from 12 countries, 15 government institutions, 20 universities, two nongovernmental organizations and 12 corporations.

RISK21 developed a conceptual framework for effective use of all relevant information for interactive and transparent evaluation of the sufficiency of exposure and hazard information to inform a risk-based decision. The result is a problem-formulation-based roadmap and a simple evaluation matrix. The overarching principles of the RISK21 approach are described by Pastoor et al. (2014) and explained in detail in Embry et al. (2014). The RISK21 approach is a problem-formulation based, exposure-driven paradigm that takes advantage of existing information and aids in identifying when additional data are needed to make a decision.

In the present article, the RISK21 matrix is used as a tool for priority setting. This approach encourages a directed evaluation of the sufficiency of available data to make conclusions about what additional data may be most useful. The RISK21 matrix organized the data evaluation and provided a framework for a directed discussion for prioritization of chemicals requiring additional data; most importantly it supported determination of what data types would add most value. The present work does not prescribe a particular method for assessing exposure or toxicity, but rather demonstrates the application of various ways of using the RISK21 approach.

## Case study overview

The RISK21 project team created this case study to evaluate the RISK21 principles, their application in prioritization of chemicals for further testing and

evaluation in the absence of comprehensive data, and the use of the proposed RISK21 roadmap and matrix (Figure 1). A companion case study (Doe et al. 2015) examined a data-rich example that estimated the risk of the “nth” pyrethroid in a class of 11 well-tested pyrethroids. The application in the present work was to use the framework as a screening tool to illustrate a resource-appropriate approach for prioritizing single chemical risk assessments based on both exposure and hazard (USEPA 2003). This case example specifies that a regulatory agency has identified 20 chemicals detected in surface water and groundwater, which could potentially appear in drinking water (Table 1). With a timeline of 1 year, a decision needs to be made whether or not risk management is indicated for the chemicals on this list as potential drinking water contaminants. For simplicity, the only route of exposure considered was consumption of drinking water. The chemicals selected were for illustrative purposes only, and the list does not represent any ongoing or anticipated hazard or risk assessment. Hence, no conclusions on actual risk, particularly of combined exposures, should be inferred. Using the proposed framework, the following specific questions were addressed.

- Which chemicals would be high priority candidates for risk management based on their potential risk to humans?
- What additional factors, such as data collection or model refinement, might be considered?
- What additional information (e.g. exposure information, toxicity information or both) would be most useful in addressing these questions?

This exercise does not go as far as determination of safety assessment or calculation of risk; rather it illustrates the application of the RISK21 approach for screening and prioritization for further data needs. This example demonstrates the utility of the RISK21 approach in effective and transparent assessment of a large number of chemicals in a short amount of time. While it might seem arbitrary, it is not unusual for a time factor to be a component of regulatory or other risk management decision making. The goal was to provide a restriction to the evaluation so that it would not be open-ended and to indicate that there was not enough time to perform new toxicology or epidemiology studies. The exercise aimed to determine how existing data can be used in a structured way to guide decision making. Thus, the RISK21 approach evaluated the appropriate use of available data to resolve the problem and determine if and what kind of additional data may be needed. It should be noted that there are, in fact, completed risk assessments for several of

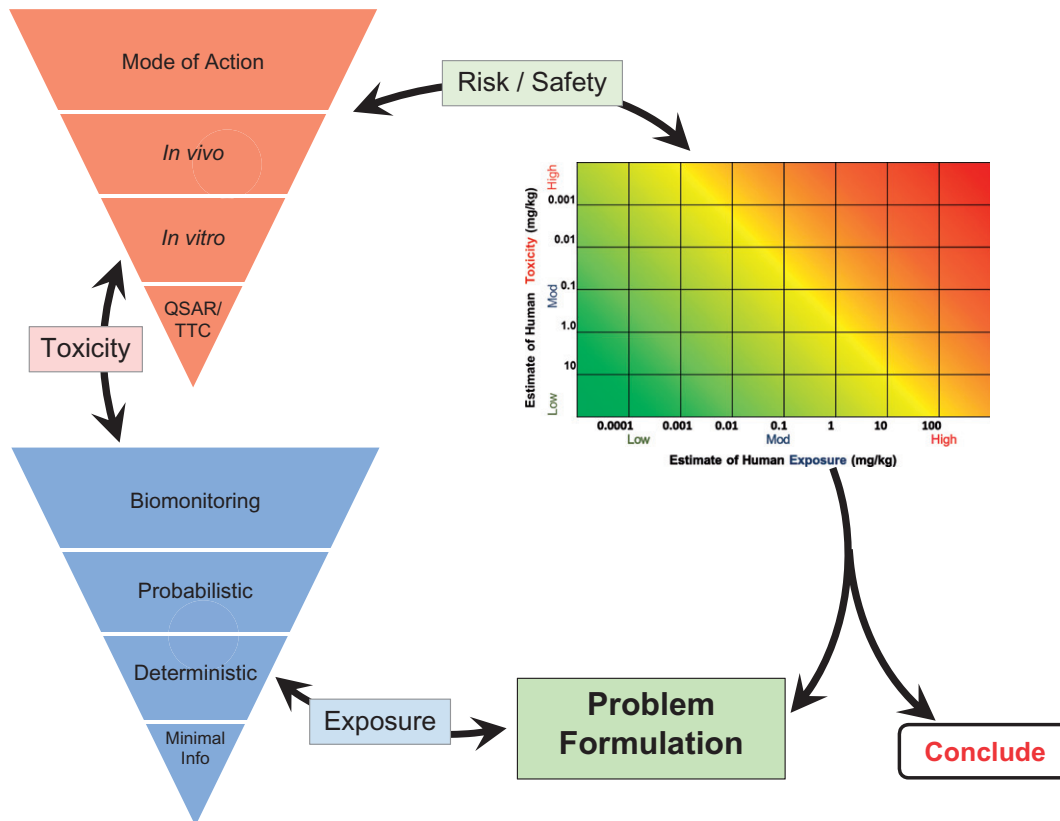


Figure 1. General conceptual framework of the RISK21 approach (Embry et al. 2014).

Table 1. Exposure estimates based on water solubility for 20 selected chemicals.

Chemical	Water solubility (mg/L)	Exposure value (based on solubility) (mg/kg bw/d)	Reference for solubility
Styrene	310	10.33	<a href="http://www.epa.gov/chemfact/styre-sd.pdf">http://www.epa.gov/chemfact/styre-sd.pdf</a>
Chlorobenzene	466.3	16.6	<a href="http://www.epa.gov/chemfact/chlor-sd.pdf">http://www.epa.gov/chemfact/chlor-sd.pdf</a>
1,4-Dioxane	1 000 000	33 333	<a href="http://www.epa.gov/chemfact/dioxa-sd.txt">http://www.epa.gov/chemfact/dioxa-sd.txt</a>
Hexachlorobenzene	0.0062	2E-04	<a href="http://water.epa.gov/drink/contaminants/basicinformation/historical/upload/Archived-Technical-Fact-Sheet-on-Hexachlorobenzene.pdf">http://water.epa.gov/drink/contaminants/basicinformation/historical/upload/Archived-Technical-Fact-Sheet-on-Hexachlorobenzene.pdf</a>
Methyl tert-butyl ether	51 000	1700	<a href="http://www.epa.gov/chemfact/s_mtbe.txt">http://www.epa.gov/chemfact/s_mtbe.txt</a>
Toluene diisocyanate	37.6	1.252	<a href="http://ntp.niehs.nih.gov/ntp/roc/content/profiles/toluenediisocyanates.pdf">http://ntp.niehs.nih.gov/ntp/roc/content/profiles/toluenediisocyanates.pdf</a>
1,2-Dibromo-3-chloropropane (DBCP)	1230	41	<a href="http://www.epa.gov/safewater/pdfs/factsheets/soc/tech/dbcp.pdf">http://www.epa.gov/safewater/pdfs/factsheets/soc/tech/dbcp.pdf</a>
Heptachlor epoxide	0.05	0.007	<a href="http://www.atsdr.cdc.gov/toxprofiles/tp12-c4.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp12-c4.pdf</a>
Picloram	430	14.33	<a href="http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/water-eau/picloram-piclorame/picloram-piclorame-eng.pdf">http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/water-eau/picloram-piclorame/picloram-piclorame-eng.pdf</a>
Oxyfluorfen	0.1	0.004	<a href="http://www.epa.gov/opp00001/chem_search/reg_actions/reregistration/red_PC-111601_1-Aug-02.pdf">http://www.epa.gov/opp00001/chem_search/reg_actions/reregistration/red_PC-111601_1-Aug-02.pdf</a>
Dimethipin	4600	153.3	<a href="http://www.agropages.com/agrodata/Detail-473.htm">http://www.agropages.com/agrodata/Detail-473.htm</a>
Chlordane	0.01	0.002	<a href="http://www.epa.gov/safewater/pdfs/factsheets/soc/tech/chlordan.pdf">http://www.epa.gov/safewater/pdfs/factsheets/soc/tech/chlordan.pdf</a>
Fenarimol	14	0.467	<a href="http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0241-0015">http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0241-0015</a>
Fenoxycarb	6	0.2	<a href="http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0111-0007">http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0111-0007</a>
Fenoxaprop-P-ethyl	0.8	0.03	<a href="http://www.syngentacropprotection.com/pdf/msds/03_482310312005.pdf">http://www.syngentacropprotection.com/pdf/msds/03_482310312005.pdf</a>
alpha-Hexachlorocyclohexane	69.5	0.243	<a href="http://www.atsdr.cdc.gov/toxprofiles/tp43-c4.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp43-c4.pdf</a>
Toxaphene	0.0000055	1E-05	<a href="http://ntp.niehs.nih.gov/ntp/roc/content/profiles/toxaphene.pdf">http://ntp.niehs.nih.gov/ntp/roc/content/profiles/toxaphene.pdf</a>
2,4,5-TP (Silvex)	71	2.367	<a href="http://nepis.epa.gov/EPA/html/Pubs/pubtitleOW.html">http://nepis.epa.gov/EPA/html/Pubs/pubtitleOW.html</a> [EPA 811-F-95-003ddT]
Quizalofop-P-ethyl	0.61	0.01	<a href="http://www.fengle-agrochem.com/2013071612375815595.pdf">http://www.fengle-agrochem.com/2013071612375815595.pdf</a>
Fomesafen sodium	50	1.667	<a href="http://www.epa.gov/pesticides/chem_search/hhbp/R180904.pdf">http://www.epa.gov/pesticides/chem_search/hhbp/R180904.pdf</a>

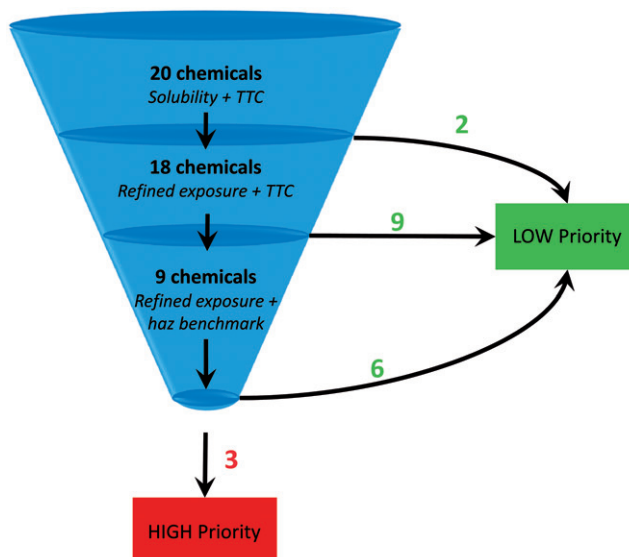


Figure 2. Overview of the case study evaluation steps.

these chemicals. Information on these existing assessments was used as a data source when needed and appropriate.

### Problem formulation

Problem formulation identifies the major factors to be considered in a specific assessment, thus informing the technical approach. An important outcome of problem formulation is a conceptual model that describes the linkages between stressors and adverse human health effects; this includes the stressor(s), exposure pathway(s), exposed lifestage(s) and population(s), and endpoint(s) that will be addressed in the risk assessment. Based on the conceptual model, an analysis plan is developed, which describes the approach for conducting the risk assessment, including its design, methods and key inputs and intended outputs.

Problem formulation establishes the purpose, scope and a plan for collecting and evaluating information, which guides effective use of resources at each stage of the assessment (Embry et al. 2014). This step helps to identify major factors that must be considered, and includes identification of the exposure scenario, availability of existing knowledge, context and assessment purpose; all of these inform the technical approach to the assessment (National Research Council 2009; USEPA 2014). The problem statement for this case study is described below.

- Scenario: Twenty chemicals that may be present in drinking water have been detected through various monitoring programs in surface and ground water.
- Existing knowledge: There is a varying amount of prior knowledge for all of the chemicals on the list

(chemical properties, exposure and biological activity); this information can and should be effectively utilized before additional data are generated.

- Context: For illustrative purposes, potential adult human exposure to these chemicals is assumed to occur only through drinking water and not through other routes.
- Purpose of the assessment: With a timeline of 1 year, a decision needs to be made regarding whether a risk management as potential drinking water contaminants is indicated for any of the chemicals on this list. The goal of this assessment is to prioritize chemicals for additional evaluation and to determine what information is needed. It is not to perform a definitive risk assessment.

A summary of the evaluation process is included in Figure 2 and described in the text below.

### First evaluation

The process is iterative and tiered in that after each evaluation of the exposure and hazard data, the evaluator can determine if sufficient information is available to make a decision or if additional data are necessary (Embry et al. 2014). In the present case, the initial focus of the evaluation was on the availability of data that would inform potential for human exposure at levels of concern.

### Estimation of exposure

Low-tier exposure estimates were calculated using individual chemical water solubility values at 25 °C. When experimental values were not available, water

solubility was estimated from Log  $K_{ow}$  (EpiSuite, WSKOWWIN v1.41; available at: <http://www.epa.gov/opptintr/exposure/pubs/episuitedi.htm>). Exposure estimates were calculated assuming adult consumption of 2 L/day drinking water and a mean body weight of 60 kg (WHO 2008).

### Estimation of toxicity

The threshold of toxicological concern (TTC) (Kroes et al. 2005; SCCS, SCHER, SCENIHR 2012) approach sets a *de minimus* value below which exposure is unlikely to be of concern, and represents a Tier 0 method, based on broad chemical categories. This approach requires an estimate of exposure in which there is reasonable confidence that it is not an underestimate. Despite a low level of precision, the TTC method of hazard characterization has value in situations wherein the exposure is very low, and therefore the risk estimate is also very low. The TTC approach has been applied globally to food safety assessments and genotoxic impurities in pharmaceuticals (for review, see Hennes 2012), and recent work has evaluated the potential application to mixtures as a Tier 0 approach (Meek et al. 2011).

The TTC approach is currently not applicable for evaluating the following: inorganic substances, metals, polymers, substances that bioaccumulate, proteins, steroids, specific structural classes which may be high potency carcinogens, substances predicted to have the potential for local effects on the gastrointestinal tract, nanomaterials, radioactive substances and essential elements (such as selenium, sodium and calcium). These types of substances would require the evaluation of available toxicity data on a case-by-case basis. This is discussed in more detail in the recent opinion from the European Food Safety Authority (EFSA) (EFSA 2012a,b). Bioaccumulation potential for low solubility chemicals should also be evaluated to ensure applicability of the TTC approach; however, this was not performed for the present evaluation.

The lowest tier approach in this example assumes that no toxicological information, other than structure, is available for the specific substances. Though additional toxicity information is available for most of the chemicals that were evaluated in the present example, for illustrative purposes the TTC approach was used as an initial tier for application of the framework. The TTC concept is described in Munro et al. (1996). Briefly, TTC values were derived using conservative points of departure (no observed effect levels (NOELs) were used), expressed as mg/kg bw per day, for chemicals within each Cramer class; this comprises a database of

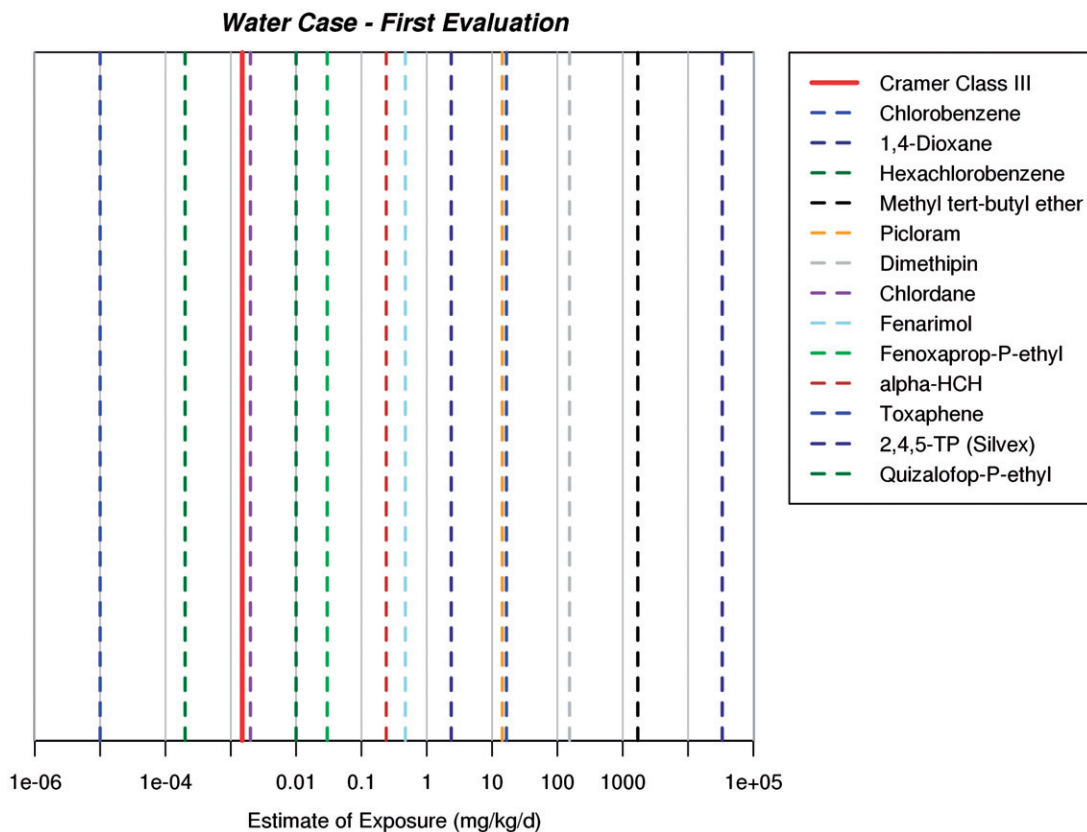
**Table 2.** Cramer classification and corresponding TTC values for the 20 selected chemicals in the case study.

Chemical	Cramer class	TTC (mg/kg/d)
Styrene	I	0.03
Chlorobenzene	III	1.5E-3
1,4-Dioxane	III	1.5E-3
Hexachlorobenzene	III	1.5E-3
Methyl tert-butyl ether	III	1.5E-3
Toluene diisocyanate	SA <sup>a</sup>	2.5E-6
1,2-Dibromo-3-chloropropane (DBCP)	SA	2.5E-6
Heptachlor epoxide	SA	2.5E-6
Picloram	III	1.5E-3
Oxyfluorfen	SA	2.5E-6
Dimethipin	III	1.5E-3
Chlordane	III	1.5E-3
Fenarimol	III	1.5E-3
Fenoxycarb	OP/Carbamates <sup>b</sup>	3E-4
Fenoxaprop-P-ethyl	III	1.5E-3
alpha-Hexachlorocyclohexane	III	1.5E-3
Toxaphene	III	1.5E-3
2,4,5-TP (Silvex)	III	1.5E-3
Quizalofop-P-ethyl	III	1.5E-3
Fomesafen sodium	SA	2.5E-6

<sup>a</sup>SA = structural alert.

<sup>b</sup>Organophosphates and carbamates were assigned a separate TTC value of 18 µg/day or 0.3 µg/kg bw per day (Kroes et al. 2004).

subchronic, chronic and reproductive/developmental oral toxicity data on more than 600 chemicals (Munro et al. 1996). The point of departure (POD) for each chemical was plotted based on Cramer structural class, and values corresponding to the 5th percentile NOEL were identified. These values were multiplied by 60 kg (average adult body weight) and divided by an uncertainty factor of 100 (i.e. default value used to establish reference doses) to calculate human exposure threshold (i.e. TTC) values of 1800 µg/day (Cramer class I), 540 µg/day (Cramer class II) and 90 µg/day (Cramer class III). For TTC values to be used for comparison using the RISK21 matrix, the TTC values were converted back into units of milligrams per kilogram of body weight per day. Accordingly, Cramer class I chemicals have human exposure threshold values of 0.03 mg/kg body weight per day; class II, 0.009 mg/kg body weight per day; and class III, 0.0015 mg/kg body weight per day (Barlow 2005). Organophosphate and carbamate insecticides were specifically evaluated by Kroes et al. (2004), which set a TTC value of 0.0003 mg/kg body weight per day for substances with anti-cholinesterase activity. This value has been accepted by the European Food Safety Authority (EFSA 2012a,b) as scientifically robust. Chemicals with structural alerts based on the Benigni/Bossa rulebase for genotoxicity, mutagenicity and carcinogenicity in ToxTree v2.6.0 are included in a separate class with a threshold value of 2.5E-6 mg/kg body weight per day (Kroes et al. 2004). For this water case example, the Cramer classification of each chemical was determined using the open-source



**Figure 3.** First evaluation. RISK21 matrix plot illustrating the use of the TTC approach. The 13 chemicals belonging to Cramer Class III (of 20 in total) are plotted to demonstrate exposure (calculated based on solubility) relative to the Cramer Class III threshold of  $1.5E-3$  and which chemicals (toxaphene & HCB) fall below this value of  $3 \mu\text{g}/\text{kg}/\text{day}$ . (This illustrates the flexibility of the RISK21 matrix approach.)

program ToxTree v2.6.0 (Patlewicz et al. 2008) and the corresponding TTC value was used as a hazard benchmark (Table 2).

### Conclusions from first evaluation

Using this low-tier approach, potential drinking water exposure estimates for two chemicals (hexachlorobenzene and toxaphene) were one to two orders of magnitude below the applicable TTC hazard benchmark when solubility was used to estimate maximum potential exposure. Both of these chemicals are Cramer Class III and are plotted on a modification of the full RISK21 matrix with the other chemicals within that class (Figure 3). The matrix was adapted in order to apply the TTC as a low-tier prioritization and screening approach that uses only chemical structure and exposure information. This figure also illustrates the flexibility and utility of this framework in representing hazard or exposure data for any type of assessment to rapidly answer a variety of questions.

These two chemicals with very low solubility would result in very low potential exposure in drinking water. In

addition, sorption limits their migration to groundwater and surface water, and water treatment processes remove hydrophobic chemicals during treatment. The use of measured solubility values minimized false negatives and increased confidence in the evaluation.

### Second evaluation

After determining that two of the 20 chemicals were deemed low priority for risk management from the low-tier assessment (based on water solubility and TTC), the remaining 18 chemicals were further evaluated.

### Estimation of exposure

Whereas in the first stage of exposure evaluation only solubility was used to estimate potential drinking water exposure, in the subsequent stage models were used to provide a more precise estimate. All of the chemicals on the list have existing exposure information available from various data sources. Many have been previously assessed by various governmental agencies wherein deterministic model estimates have been generated. In

some cases, summary monitoring data (from drinking water, surface water or groundwater) have been used to estimate potential drinking water exposures. In the present work, a specific evaluation of each exposure model and its relative quality was not performed. Rather, as the objective was to evaluate the utility of the RISK21 framework, information from readily available exposure models was collected. While there is some variability in the relative quality of the available data sourced for the present effort they are adequate for these illustrative purposes. The exposure estimates thus obtained are shown in Table 3 for the 18 chemicals remaining.

### **Estimation of toxicity**

For this assessment, TTC values (as described above) were used as the toxicity estimates.

### **Conclusions from second evaluation**

In this second evaluation (Table 3), exposure to nine of the remaining 18 chemicals is below the applicable TTC hazard benchmark when using the updated exposure estimates, in some cases by several orders of magnitude. Therefore, these nine chemicals were deemed low priority for additional evaluation.

## **Third evaluation**

### **Estimation of exposure**

Exposure values from the second assessment were used.

### **Estimation of toxicity**

#### **Information gathering**

A core principle of the RISK21 approach is to utilize all available relevant scientific information to determine if additional data are needed before a decision can be made. For the case study, toxicity information was aggregated from existing data sources. These included publicly available information used for assessments published by the organizations listed below; they were accessed either directly through organization websites or through secondary sites identified by general web searching. The case study authors understand that good risk assessment practice encourages the scrutiny and re-evaluation of existing data based on current scientific understanding and thus we encourage such evaluation.

- California EPA (including Department of Pesticide Regulation)
- US Centers for Disease Control, ATSDR
- European Food Safety Authority

- European Chemicals Agency (ECHA; formerly ECB)
- European Medicines Agency (EMA)
- European Union Review Reports
- Health Canada (including Pest Management Regulatory Agency (PMRA))
- Joint FAO/WHO Meeting on Pesticide Residues (JMPR)
- National Toxicology Program
- OECD
- US Consumer Product Safety Commission
- USEPA
- IRIS
- Pesticide tolerances
- Pesticide risk assessments
- WHO Joint Expert Committee on Food Additives (JECFA)
- Others: (standard PubMed and GOOGLE search using common chemical name)

The current information gathering exercise was not a systematic, thorough data review. The exercise was, however, an effective and efficient way to gather available information to determine if there were sufficient data to make a decision. After initial evaluation of the available data one can then make a determination if a more exhaustive search for toxicity data is needed or if additional data generation would be necessary for the assessment to be of value for decision-making. Of the chemicals evaluated in the present example, the nine that remained after the first two evaluations had readily accessible and adequate data to inform the decision process.

### **Use of the matrix**

The toxicity values retrieved and used in the present example were, in most instances, animal chronic NOEL or no adverse effect level (NOAEL values) rather than RfDs, ADIs or other calculated values with safety or uncertainty factors applied. However, the NO(A)EL values chosen were, in most cases, those used to derive RfD or ADI values, if available. The RISK21 approach, through the use of the matrix, allows transparent visualization of the available information. Judgments concerning the appropriate cutoff values for decision-making (e.g. where the green zone on the matrix lies) should be made in the problem formulation phase and are not reflected when plotting information on the matrix. While the matrix is sufficiently flexible to enable the reviewer to apply additional criteria, such as uncertainty factors, into the evaluation, those are not necessary when using data for priority setting. In the present case, the toxicity data were used directly on the matrix and in the evaluation to inform the

**Table 3.** Refined exposure values and corresponding TTC hazard bench marks for 18 remaining chemicals in the case study.

Chemical	Refined exposure estimate based on available information (mg/kg bw/d)	Exposure data source	TTC (mg/kg/d)
Styrene*	5.7E-5	ECHA Monitoring Data <a href="http://echa.europa.eu/documents/10162/a05e9fc2-eaf7-448e-b9b2-d224d28173c0">http://echa.europa.eu/documents/10162/a05e9fc2-eaf7-448e-b9b2-d224d28173c0</a>	0.03
	1.7E-6	EUSES Modeling Results <a href="http://echa.europa.eu/documents/10162/a05e9fc2-eaf7-448e-b9b2-d224d28173c0">http://echa.europa.eu/documents/10162/a05e9fc2-eaf7-448e-b9b2-d224d28173c0</a>	
Chlorobenzene	3.3E-3	Maximum reported monitoring concentration summarized in ATSDR Tox Profile <a href="http://www.atsdr.cdc.gov/toxprofiles/tp131-c5.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp131-c5.pdf</a>	1.5E-3
1,4-Dioxane*	4.3E-5	Regional PEC (EUSES model) <a href="http://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa">http://echa.europa.eu/documents/10162/a4e83a6a-c421-4243-a8df-3e84893082aa</a>	1.5E-3
Methyl tert-butyl ether	0.767	Max value from JRC 2002 monitoring report <a href="http://www.efoa.eu/documents/document/20100715150023-mtbe_-_eu_risk_assessment_report_-_2002.pdf">http://www.efoa.eu/documents/document/20100715150023-mtbe_-_eu_risk_assessment_report_-_2002.pdf</a>	1.5E-3
Toluene diisocyanate	0.8	REACH ERC1 worst case local surface water estimate	2.5E-6
1,2-Dibromo-3-chloropropane (DBCP)	1.3E-5	Well monitoring data (max), NJ, USA Referenced in: <a href="http://sd.water.usgs.gov/nawqa/pubs/journal/Rowe.EnvHealthPersp.pdf">http://sd.water.usgs.gov/nawqa/pubs/journal/Rowe.EnvHealthPersp.pdf</a>	2.5E-6
	7.0E-4	ECETOC TRA modeled value (ERC 10b)	
Heptachlor epoxide	1E-3	ECETOC TRA modeled value (ERC 10b)	2.5E-6
	3.3E-12	Range from summary of surface/groundwater monitoring data (WHO, 2006)	
	9.3E-4	<a href="http://www.who.int/ipcs/publications/cicad/cicad70.pdf">http://www.who.int/ipcs/publications/cicad/cicad70.pdf</a>	
Picloram	2.9E-7	Range of drinking water detection values from USDA PDP dataset (2010) <a href="http://www.ams.usda.gov/AMSv1.0/pdp">http://www.ams.usda.gov/AMSv1.0/pdp</a>	1.5E-3
	5.4E-3	PRZM-EXAMS model estimate (USEPA RED) <a href="http://www.epa.gov/pesticides/reregistration/REDS/oxyfluorfen_red.pdf">http://www.epa.gov/pesticides/reregistration/REDS/oxyfluorfen_red.pdf</a>	
Oxyfluorfen	2.4E-4	FIRST model results (USEPA RED) <a href="http://www.epa.gov/pesticides/reregistration/REDS/dimethipin_red_final.pdf">http://www.epa.gov/pesticides/reregistration/REDS/dimethipin_red_final.pdf</a>	2.5E-6
Dimethipin*	2.4E-4	FIRST model results (USEPA RED) <a href="http://www.epa.gov/pesticides/reregistration/REDS/dimethipin_red_final.pdf">http://www.epa.gov/pesticides/reregistration/REDS/dimethipin_red_final.pdf</a>	1.5E-3
Chlordane*	1.4E-4	Monitoring data – highest reported mean ATSDR Tox Profile <a href="http://www.atsdr.cdc.gov/toxprofiles/tp31-c5.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp31-c5.pdf</a>	1.5E-3
Fenarimol	2.2E-3	PRZM-EXAMS model estimate (USEPA) <a href="http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0241-0003;oldLink=false">http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0241-0003;oldLink=false</a>	1.5E-3
Fenoxycarb*	3.3E-6	PEARL 3.3.3 and PELMO 3.3.213 model estimate <a href="http://www.efsa.europa.eu/en/efsajournal/doc/1779.pdf">http://www.efsa.europa.eu/en/efsajournal/doc/1779.pdf</a>	3E-4
Fenoxaprop-P-ethyl*	4E-6	Health Canada PMRA 2004 model results	1.5E-3
	7E-6	<a href="http://publications.gc.ca/collections/collection_2011/sc-hc/H113-27-2011-4-eng.pdf">http://publications.gc.ca/collections/collection_2011/sc-hc/H113-27-2011-4-eng.pdf</a>	
alpha-Hexachlorocyclohexane*	0.5E-6	ATSDR Tox Profile	1.5E-3
	1E-6	<a href="http://www.atsdr.cdc.gov/toxprofiles/tp43.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp43.pdf</a>	
2,4,5-TP (Silvex)*	3.3E-6	Detection value from a public well in NC - Wade et al., 1998; referenced in: <a href="http://oehha.ca.gov/water/phg/pdf/SilvexPHG92403.pdf">http://oehha.ca.gov/water/phg/pdf/SilvexPHG92403.pdf</a>	1.5E-3
Quizalofop-P-ethyl*	6.6E-5	PRZM-EXAMS/SCI-GROW model estimate (groundwater) (USEPA) <a href="http://www.gpo.gov/fdsys/pkg/FR-2012-04-20/html/2012-9447.htm">http://www.gpo.gov/fdsys/pkg/FR-2012-04-20/html/2012-9447.htm</a>	1.5E-3
Fomesafen sodium	3E-4	PRZM-EXAMS model estimate (USEPA) - maximum annual average concentration value (surface water) <a href="http://www.epa.gov/pesticides/chem_search/hhbp/R180904.pdf">http://www.epa.gov/pesticides/chem_search/hhbp/R180904.pdf</a>	2.5E-6

Chemicals marked with an asterisk indicate those which were not deemed high-priority after the second evaluation.

determine whether sufficient data were available to prioritize the need for risk management. To complete the current exercise it was not necessary to complete the risk assessments, but only to illustrate the path one could take to do so. Values used are provided in Table 4.

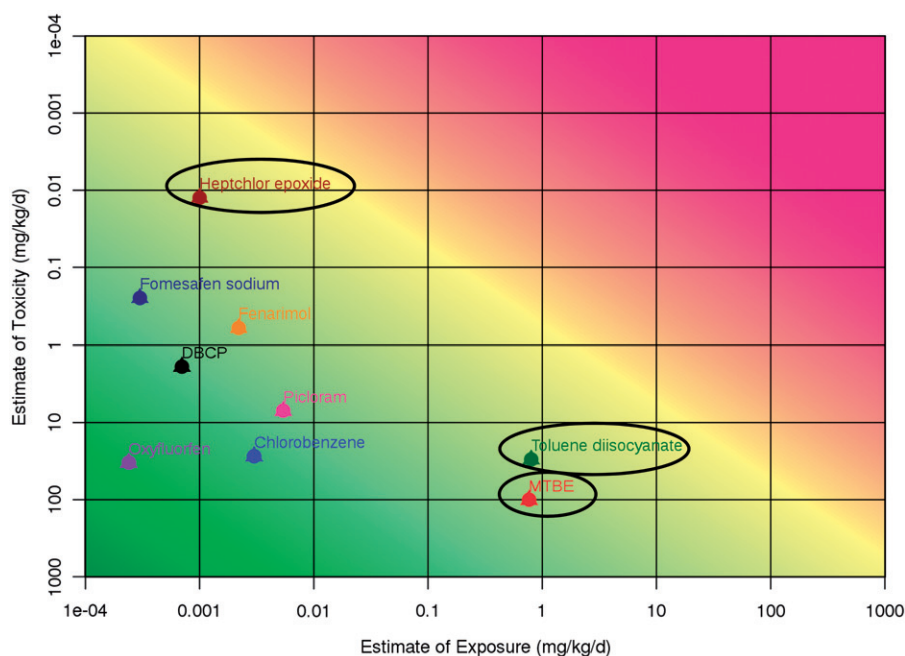
### Prioritization decision

The nine chemicals remaining after the second evaluation were further assessed by comparing the exposure model estimates to available toxicity information (see section above for methodology). The values and their



**Table 4.** Updated exposure values and available toxicity values for nine remaining chemicals in the case study.

Chemical	Refined exposure estimate (from Table 3) (mg/kg bw/d)	Available toxicity value	Toxicity data source
Chlorobenzene	3E-3	NOAEL = 27.25 mg/kg/d	<a href="http://www.epa.gov/chemfact/chlor-sd.pdf">http://www.epa.gov/chemfact/chlor-sd.pdf</a>
Methyl tert-butyl ether	0.767	NOAEL = 100 mg/kg/d	<a href="http://www.epa.gov/chemfact/s_mtbe.txt">http://www.epa.gov/chemfact/s_mtbe.txt</a>
Toluene diisocyanate	0.8	FEL = 30 mg/kg/d	<a href="http://www.epa.gov/iris/subst/0503.htm">http://www.epa.gov/iris/subst/0503.htm</a>
1,2-Dibromo-3-chloropropane (DBCP)	7E-4	LOAEL = 1.88 mg/kg/d	<a href="http://www.atsdr.cdc.gov/toxprofiles/tp36.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp36.pdf</a>
Heptachlor epoxide	1E-3	LOAEL = 0.0125 mg/kg/d	<a href="http://www.atsdr.cdc.gov/toxprofiles/tp12-c8.pdf">http://www.atsdr.cdc.gov/toxprofiles/tp12-c8.pdf</a>
Picloram	2.9E-75.4E-03	NOEL = 7 mg/kg/d	<a href="http://oehha.ca.gov/water/phg/pdf/picr2_c.pdf">http://oehha.ca.gov/water/phg/pdf/picr2_c.pdf</a>
Oxyfluorfen	2.4E-4	LOAEL = 33 mg/kg/d	<a href="http://www.epa.gov/oppsrrd1/REDS/oxyfluorfen_red.pdf">http://www.epa.gov/oppsrrd1/REDS/oxyfluorfen_red.pdf</a>
Fenarimol	2.2E-3	NOAEL = 0.6 mg/kg/d	<a href="http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0241-0003;oldLink=false">http://www.regulations.gov/#!documentDetail;D=EPA-HQ-OPP-2006-0241-0003;oldLink=false</a>
Fomesafen sodium	3E-4	NOAEL = 0.25 mg/kg/d	<a href="http://www.epa.gov/pesticides/chem_search/hhbp/R180904.pdf">http://www.epa.gov/pesticides/chem_search/hhbp/R180904.pdf</a>

**Figure 4.** Third evaluation. Matrix plot of the nine remaining chemicals (point estimates for both exposure and toxicity). Those circled are the three designated high priority for further evaluation based on proximity to the yellow zone.

corresponding sources are noted in Table 4, and the results are shown in Figure 4 and represented as point estimates for comparison purposes.

In the present evaluation, the yellow zone of the matrix was not specifically calibrated to adjust for a particular margin of exposure as might be done when evaluating for a risk assessment. This margin was set at 1:1, since the goal of the approach is to prioritize chemicals for further evaluation, rather than to make a definitive risk decision. The utility of additional data

would be determined by the distance (horizontally and vertically) from the yellow zone. Where the distance between the green and yellow zones is large in both dimensions, i.e. low toxicity and low exposure, the decision may be that this chemical is a low priority for further evaluation. An example shown in Figure 4 is oxyfluorfen. Where there are several chemicals close to the yellow zone, the exposure and toxicity distance can inform where the greater priority is for further information. Examples shown in Figure 4 are toluene

diisocyanate, heptachlor epoxide and MTBE. Similarly, the relative distance of compounds to each other in the two dimensions will assist in prioritization and resource allocation. The evaluation of the final nine chemicals illustrate that three chemicals would be listed as high priority due to their proximity to the yellow zone: toluene diisocyanate, heptachlor epoxide and MTBE.

## General conclusions

The present example illustrates the broad utility and flexibility of the RISK21 approach and framework. This framework provides an organized and transparent strategy to concurrently evaluate available exposure and hazard data to determine when sufficient information is available to make a decision and when additional data would be needed to finalize the safety assessment. Using the RISK21 framework allowed determination of which chemicals could rapidly be deemed of low priority for further consideration based on readily accessible data such as water solubility and existing TTC values. The present example indicated that additional toxicology studies on those compounds would not have provided sufficient value of information to have had impact on the decision for further consideration. Utilizing the framework, we assigned low priority to 11 of the 20 chemicals based on available exposure data alone. We then were able to utilize refined hazard estimates to evaluate the remaining nine chemicals, determining that six were lower priority and three were higher priority. During the development and evaluation of the data used in the present case of potential drinking water contaminants, the evaluation team identified that improved exposure models or measurements would have provided greater value for this analysis had they been available rather than additional hazard data.

The RISK21 roadmap and matrix were clearly fit for the purpose of supporting determination of whether sufficient information was available to address the problem formulated. For those chemicals deemed to have insufficient information, the RISK21 approach readily identified the type of information that would be of greatest value. The most significant drawback was not in the Framework but rather the availability of appropriate exposure models.

The matrix enabled rapid evaluation of the relative adequacy of the available data for each chemical compared to other chemicals in this group. An automated graphing function as a web-based application has been developed (available at [www.risk21.org/](http://www.risk21.org/)); this facilitates the speed, consistency and efficiency of matrix construction. The framework was also very flexible in its application in that the nature of the

graph could be readily modified to suit the specific question being asked. For example if one wanted to compare relative exposure based only on water solubility, then information on toxicity would not initially be necessary, as toxicity would be represented by the respective TTC values. In this instance only exposure is plotted, on the x-axis, with no chemical specific toxicity data on the graph (see Figure 3). This simple approach enabled two chemicals to be designated as low priority. Using the RISK21 iterative approach provided a means for rapid and efficient focus on the progressively smaller sub-sets of chemicals that were of the greater concern.

The most significant rate limiting step in constructing the graphs was the availability of appropriate data in accessible data and knowledge bases. Accessibility of suitable data to graph on the matrix is necessary to reach the necessary conclusions for the risk decision. Access to large data sets of this quality will ultimately prevent redundant and unnecessary studies from being conducted so that effective decisions can be made with speed, confidence and accuracy. However, it is clear that the RISK21 visualization tool greatly enhanced the ability to evaluate and prioritize data needs across a large group of chemicals.

## Acknowledgements

The authors gratefully acknowledge the government, academic and industry scientists of the HESI RISK21 Technical Committee for their contributions to this work. A full list can be accessed at [www.risk21.org](http://www.risk21.org). The comments of four reviewers selected by the Editor and anonymous to the authors were helpful in revising the article.

## Declaration of interest

The authors' affiliations are as shown on the cover page. The authors had sole responsibility for the writing and content of the article. The views and opinions expressed in the article are those of the authors, and do not necessarily reflect the views of the authors' employers or the opinions or policies of the US EPA. Mention of trade names does not constitute endorsement. None of the authors has recently or is currently involved as an expert witness in litigation or formal government rule-making on the subject of this article. None of the authors received financial support or an honorarium in the preparation of this article. The authors declare that there are no conflicts of interest.

## References

- Barlow S. Threshold of toxicological concern (TTC) – a tool for assessing substances of unknown toxicity present at low levels in the diet. ILSI Europe Concise Monograph Series. Brussels, Belgium; 2005. Available at: <http://www.ilsis.org/Europe/Pages/ViewItemDetails.aspx?WebId=84D7FA4A-0FD5->

- 40CD-A49A-2DA6FCDFD654&ListId=0348EB34-DF85-49DD-9ADE-77ED136643F1&ItemID=119 [accessed 20 June 2015].
- Council of Canadian Academies. Integrating emerging technologies into chemical safety assessment. Ottawa, Canada: Council of Canadian Academies; 2012.
- Cramer GM, Ford RA, Hall RL. Estimation of toxic hazard – a decision tree approach. *Food Cosmet Toxicol* 1978;16:255–276.
- Doe JE, Lander D, Doerr NG, Heard N, Hines RN, Lowit AB, Pastoor TP, et al. Use of the RISK21 roadmap and matrix: human health risk assessment of the use of a pyrethroid in bed netting. In preparation, 2015.
- EFSA. Draft scientific opinion on exploring options for providing preliminary advice about possible human health risks based on the concept of threshold of toxicological concern (TTC). *EFSA J* 2012a;10:2750.
- EFSA. EFSA Panel on Plant Protection Products and their Residues (PPR); Scientific opinion on evaluation of the toxicological relevance of pesticide metabolites for dietary risk assessment. *EFSA J* 2012b;10:2799.
- Embry M, Bachman A, Bell D, Boobis A, Cohen, S, Dellarco M, Dewhurst I et al. The Risk Assessment in the 21st Century (RISK21): roadmap and matrix. *Crit Rev Toxicol* 2014;44 (Suppl 3):6–16.
- European Commission. SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), SCHER (Scientific Committee on Health and Environmental Risks), SCCS (Scientific Committee on Consumer Safety), Preliminary report on Addressing the New Challenges for Risk Assessment, 8 October 2012. Available at: [http://ec.europa.eu/health/scientific\\_committees/emerging/docs/scenihr\\_o\\_037.pdf](http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_037.pdf) [accessed 20 June 2015].
- Hennes EC. An overview of values for the threshold of toxicological concern. *Toxicol Lett* 2012;211:296–303.
- Kroes R, Kleiner J, Renwick AG. The threshold of toxicological concern in risk assessment. *Toxicol Sci* 2005;86:226–230.
- Meek ME, Boobis AR, Crofton KM, Heinemeyer G, Raaij MV, Vickers C. Risk assessment of combined exposure to multiple chemicals: a WHO/IPCS framework. *Regul Toxicol Pharmacol* 2011;60: S1–S14.
- Munro I, Ford RA, Kennepohl E, Sprenger JG. Correlation of a structural class with no-observed-effect levels: a proposal for establishing a threshold of concern. *Food Chem Toxicol* 1996;34:829–867.
- National Research Council. Exposure science in the 21st century: a vision and a strategy. Washington, DC: The National Academies Press; 2012.
- National Research Council. Phthalates and cumulative risk assessment the task ahead. Washington, DC: The National Academies Press; 2008.
- National Research Council. Science and decisions: advancing risk assessment. Washington, DC: The National Academies Press; 2009.
- National Research Council. Toxicity testing in the twenty-first century: a vision and a strategy. Washington, DC: The National Academies Press; 2007.
- Pastoor TP, Bachman A, Bell D, Cohen S, Dellarco M, Dewhurst I, Doe J, et al. A 21st century roadmap for human health risk assessment. *Crit Rev Toxicol* 2014;44 (Suppl 3):1–5.
- Patlewicz G, Jeliakova N, Safford RJ, Worth AP, Aleksiev B. An evaluation of the implementation of the Cramer classification scheme in the Toxtree software. *SAR QSAR Environ Res* 2008;19:495–524.
- SCCS, SCHER, SCENIHR. Joint opinion on the use of the threshold of toxicological Concern (TTC) approach for human safety assessment of chemical substances with focus on cosmetics and consumer products, 8 June 2012. Available at: [http://ec.europa.eu/health/scientific\\_committees/consumer\\_safety/docs/sccs\\_o\\_092.pdf](http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_092.pdf) [accessed 20 June 2015].
- Toccalino PL, Norman JE. Health-based screening levels to evaluate U.S. Geological Survey ground-water quality data. *Risk Anal* 2006;26:1339–1348.
- USEPA. A Framework for a Computational Toxicology Research Program in ORD. U. S Environmental Protection Agency, Office of Research and Development, EPA/600/R-03/065; 2003.
- USEPA. Framework for Human Health Risk Assessment to Inform Decision Making. EPA/100/R-14/001. Washington, D.C.: Risk Assessment Forum, Office of the Science Advisor, USEPA; 2014. <http://www.epa.gov/raf/files/hhra-framework-final-2014.pdf> [accessed 20 June 2015].
- World Health Organisation (WHO). Guidelines for drinking-water quality – third edition incorporating the first and second addenda; 2008. Available at: [http://www.who.int/water\\_sanitation\\_health/dwq/gdwq3rev/en/](http://www.who.int/water_sanitation_health/dwq/gdwq3rev/en/). [accessed 20 June 2015]