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Coordination Action

D1.3 Second annual review of research and best practice

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PU	Public	X
PP	Restricted to other programme participants (including the Commission Services)	
RE	Restricted to a group specified by the consortium (including the Commission Services)	
CO	Confidential, only for members of the consortium (including the Commission Services	

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PREFACE

In this document we report the results of the second HENVINET evaluation of the quality of methodologies, findings and conclusions of relevant ongoing and recently completed research projects on the causal relation between environmental stressors and human health.

The results of any evaluation will be greatly influenced by the criteria applied to perform the evaluation. Developing a framework for the assessment of knowledge quality and the identification of knowledge gaps is an on-going task within the HENVINET project. The first version of the HENVINET evaluation framework was presented in deliverable 1.1 "*Framework for information gathering – evaluation of research and best practices*", and a revision of the framework was proposed in deliverable 1.2 "*First annual review of research and best practice*".

The goal of this report is to document how this revised framework was implemented in the different case study topic groups of the HENVINET project, and to report some of the first results available.

The report is structured in two parts. Part A provides an introduction to the HENVINET evaluation methodology. Part B presents an example of how the methodology was implemented in the Deca-BDE case study, through the different steps. Annex 1 presents the initial evaluation questionnaires used in all of the case studies to date. Annex 2 presents the report presents the results of the first evaluation questionnaires for the case studies on Deca-BDE, HBCD, Phthalates, Chloropyrifos, and Asthma and allergies. And finally, Annex 3 presents all available workshops reports to date, which are HBCD, Chloropyrifos and Phthalates.

The current status of the work in WP 1 is as follows:

- The brominated flame retardants decaBDE and HBCD:
  - Causal diagram and on-line evaluation tool completed
  - Tool used to perform evaluation by a group of ~20 experts
  - Follow-up questionnaire completed by a select group of experts
  - Follow-up workshop held with select group of experts to discuss and reflect on the results of the 2 questionnaires
  - For each of the 2 substances, 2 publications are under preparation:
    - Policy brief aimed at decision makers, policy makers and stakeholders
    - Academic publication aimed at researchers
- Phthalates:
  - Causal diagram and on-line evaluation tool completed
  - Tool used to perform evaluation by a group of ~20 experts
  - Follow-up questionnaire completed by a select group of experts
  - Follow-up workshop held with select group of experts to discuss and reflect on the results of the 2 questionnaires
  - 2 publications are under preparation:
    - Policy brief aimed at decision makers, policy makers and stakeholders
    - Academic publication aimed at researchers

- The impacts of climate change on asthma and other respiratory disorders
  - Causal diagram and on-line evaluation tool completed
  - Tool used to perform evaluation by a group of ~20 experts
  - Follow-up questionnaire completed by a select group of experts
  - Follow-up workshop held with select group of experts to discuss and reflect on the results of the 2 questionnaires
  - 2 publications are under preparation:
    - Policy brief aimed at decision makers, policy makers and stakeholders
    - Academic publication aimed at researchers
- The pesticide CPF
  - Causal diagram and on-line evaluation tool completed
  - Tool used to perform evaluation by a group of ~20 experts
  - Follow-up questionnaire completed by a select group of experts
  - Follow-up workshop held with select group of experts to discuss and reflect on the results of the 2 questionnaires
  - 2 publications are under preparation:
    - Policy brief aimed at decision makers, policy makers and stakeholders
    - Academic publication aimed at researchers
- The influence of environment health stressors on cancer induction
  - Causal diagram and on-line evaluation tool completed
  - Expert evaluation under preparation
- Nano particles
  - Causal diagram completed
  - On-line evaluation tool under preparation

PART A: INTRODUCTION TO THE HENVINET EVALUATION METHODOLOGY

STEPS IN THE KNOWLEDGE EVALUATION PROCESS

The HENVINET approach to knowledge quality evaluation is based on a general 3 step methodology:

1. Establish a causal diagram to identify the knowledge which is relevant to assess, i.e. the knowledge pertaining to key parameters in the cause-effect relationship between a given environmental stressor and a given health impact;
2. An expert elicitation is conducted, whereby individual experts apply knowledge quality evaluation criteria to the parameters identified in Step 1;
3. The results of Step 2 are analyzed and discussed in the context of an expert workshop. The focus of the discussion is on:
   - Identifying areas where experts agree that the quality of the knowledge available is particularly low;
   - Identifying areas where experts disagree on the quality of the knowledge available and explaining the basis for this disagreement;
   - Prioritizing the different parameters identified in the causal diagram;
   - Identifying the action justified by the information available;
   - Assessing the extent to which decisive knowledge is likely to become available in the near future;
   - Assessing the extent to which policy action could effectively deal with the problem at hand.

INTRODUCING CAUSAL DIAGRAMS

To identify relevant knowledge, it is useful to "map" the knowledge required by establishing a "mental model" or "causal diagram" illustrating all of the parameters and relationships that are suspected to be involved when a given (group of) environmental health stressor(s) leads to a given health impact. A generic example of such a diagram is illustrated in figure 1 below. More specific diagrams should be developed for specific health stressors and impacts.

The causal diagrams used in the HENVINET evaluations were all developed by the members of the HENVINET topic groups.

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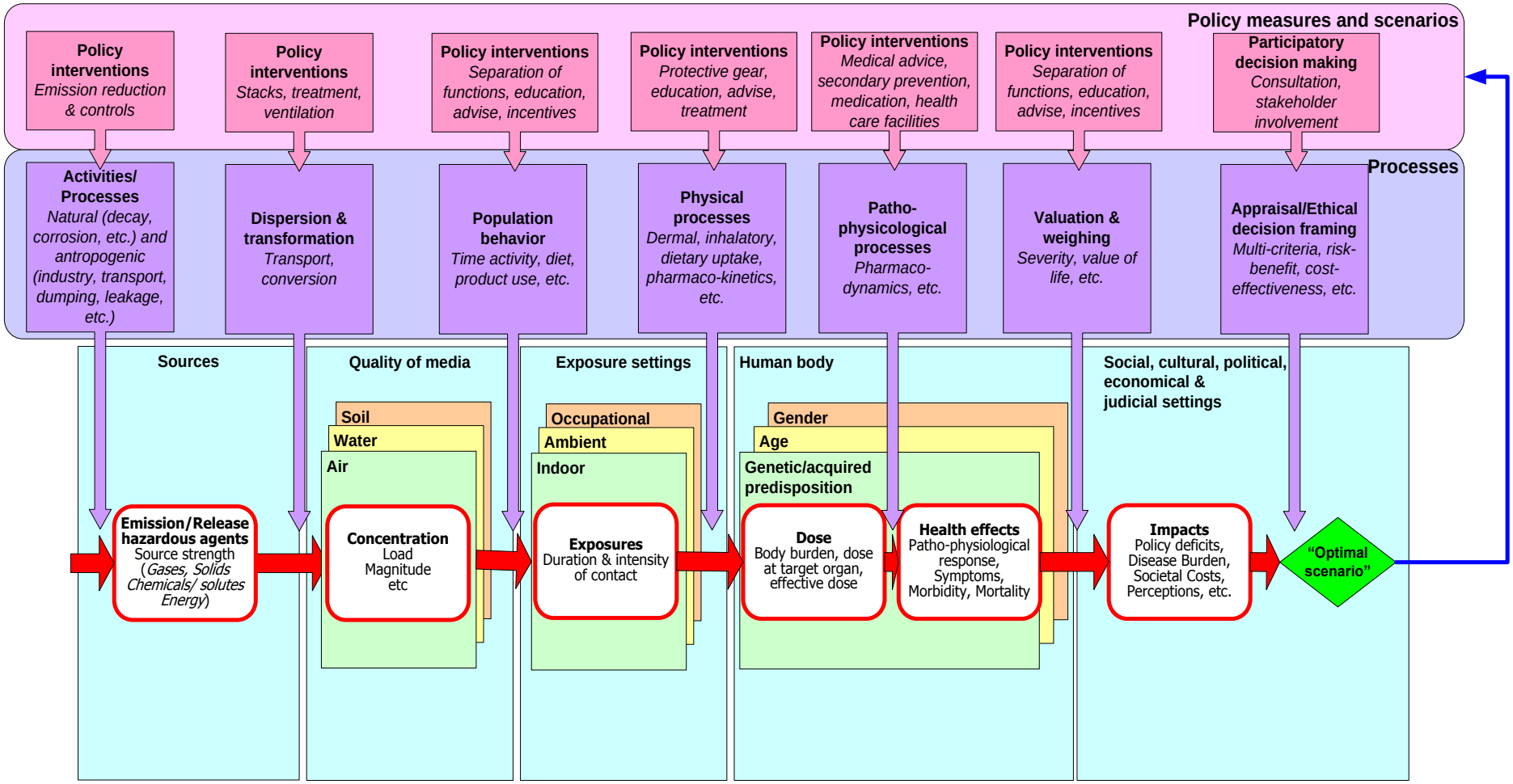


Figure 1: Generic causal diagram of relationship between environmental health stressors and health impacts (Source: Lebret et al., 2007)

CRITERIA FOR KNOWLEDGE EVALUATION

Because the HENVINET project deals with knowledge for policy, we propose that in addition to the type of quality parameters conventionally applied in research science, HENVINET must seek to evaluate the extent to which the various actors in a given policy process accept the knowledge available as a legitimate source of reference for policy making.

Following the experiences during the first annual review of research and best practice, the decision was made to consolidate the many knowledge quality criteria used at the time into a less complex "confidence" criterion, inspired by the one used by the IPCC in the AR4 series of reports (IPCC, 2007), which is as follows:

4	**3**	**2**	**1**	**0**
Very high confidence.	High confidence.	Medium confidence.	Low confidence.	Very low confidence.
At least a 9 out of 10 chance of being correct.	At least an 8 out of 10 chance of being correct.	At least a 5 out of 10 chance of being correct.	At least a 2 out of 10 chance of being correct.	Less than a 1 out of 10 chance of being correct.

PART B: EXAMPLE OF THE KNOWLEDGE EVALUATION METHOD USED BY THE HENVINET TOPIC GROUPS: THE DECA-BDE CASE STUDY

STEP 1: EVALUATION QUESTIONNAIRE:

PRELUDE

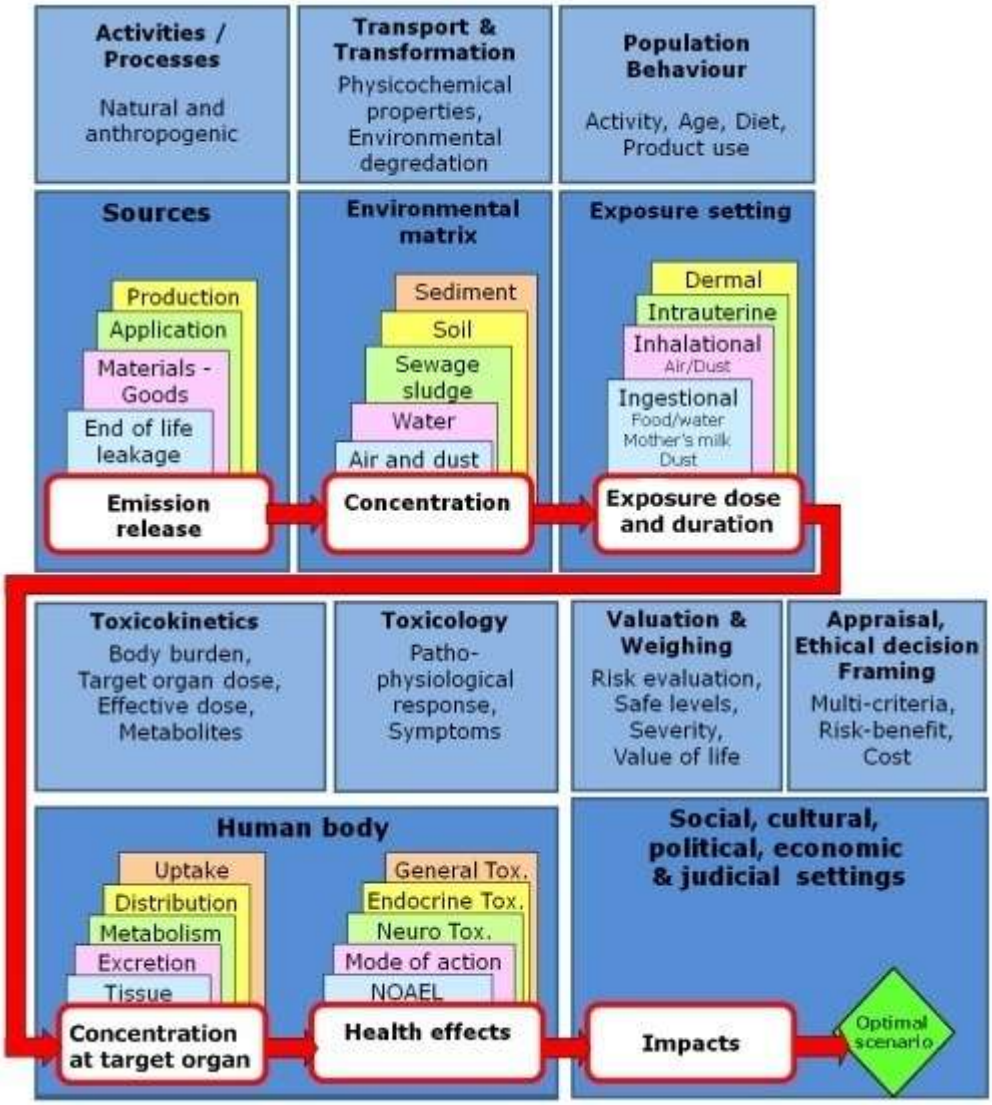
Please tell us about your research background and current institutional affiliation. These data will be confidential.

- Name:_____
- Email address: _____
- Institutional affiliation: _____
- 5 keywords describing your area of expertise:

1._____ 2._____ 3._____ 4._____ 5._____

Part A - Evaluation of the structure and completeness

The diagram shown in the figure below illustrates the cause-effect relationship between production and emission of decaBDE and health effects. For a summary explanation of the scientific basis of the diagram, please see Annex 1.



Does the diagram take into account all of the important parameters when evaluating the risks related to production, use and discharge of decaBDE?* YES/NO

If you said no to the previous question, Please explain:

Are the different causal relationships adequately structured?* YES/NO

If you said no to the previous question, Please explain:

Are there any unnecessary parameters shown in the diagram that could be deleted?* YES/NO

If you said yes to the previous question, Please explain:

PART B - EVALUATION OF INDIVIDUAL CAUSAL ELEMENTS

In the questions that follow you will be asked to express your confidence in scientists' ability to predict the concentrations, exposure and effects of decaBDE/BDE-209. Insert a check mark where you feel it is appropriate.

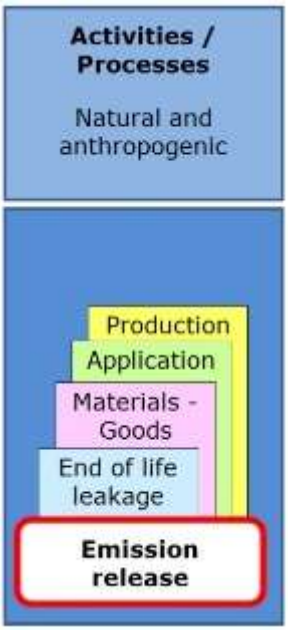
It is important that you consider each question independently of the others. For example, when you answer a question on excretion, do not take into consideration your confidence in the scientists' ability to predict absorption.

Where questions ask for your confidence level, please use these guidelines:

Very high confidence. At least 9 in 10 chance of being correct.	High confidence. At least 7 in 10 chance of being correct.	Medium confidence. At least 5 in 10 chance of being correct.	Low confidence. At least 3 in10 chance of being correct.	Very low confidence. Less than 2 in 10 chance of being correct.

Both terms decaBDE and BDE-209 are used in the evaluation form, it is aimed at using decaBDE for the technical mixture and BDE-209 for the single congener.

Sources



1. **Regarding decaBDE, what is your level of confidence in the quality of the current scientific data on:**

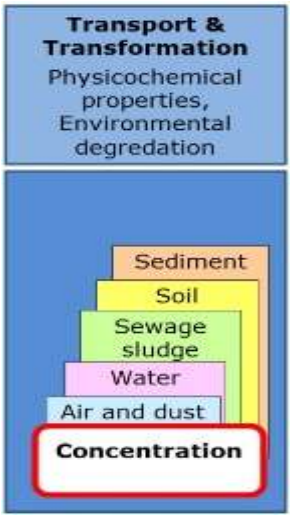
   a) Production volumes* b)Application volumes*

2. **Regarding the use of decaBDE in products, what is your level of confidence in the scientists' ability to:**

   a) Identify and quantify all different applications*

   b) Predict the magnitude of emission/release/leakage during production, use and recycling*

Environmental matrix



3. Regarding BDE-209, what is your level of confidence in the scientists' ability to predict:

   a) Environmental transformation, such as debromination, and biological half-lives?*

   b) The magnitude of long-range transport?*

4. What is your level of confidence in the scientists' ability to predict the concentration of BDE-209 in:

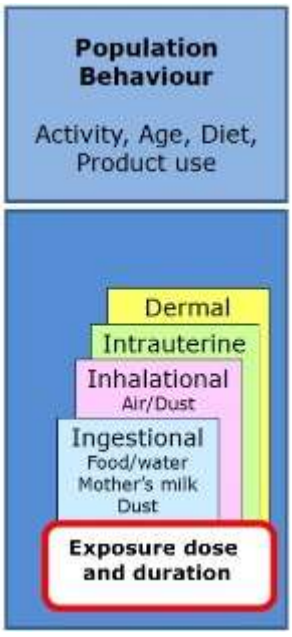
a) Sediments?* b) Sewage sludge?*

c) Soil?* d) Water?*

e) Dust?* f) Indoor Air?*

g) Outdoor Air?*

Exposure



5. What is your level of confidence in the scientists' ability to predict the level of exposure to BDE-209 in:

   a) The general population?* b) Occupationally exposed?*

   c) Infants and children?*

6. What is your level of confidence in the scientists' ability to predict the main sources of exposure to BDE-209 in:

   a) The general population?* b) Occupationally exposed?*

   c) Infants and children?*

7. What is your level of confidence in the scientists' ability to predict the exposure of the general population to BDE-209 via the following routes:

   a) Direct contact/dermal?* b) Inhalation?*

   c) Ingestion?*

8. What is your level of confidence in the scientists' ability to predict the exposure of occupationally exposed groups to BDE-209 via the following routes:

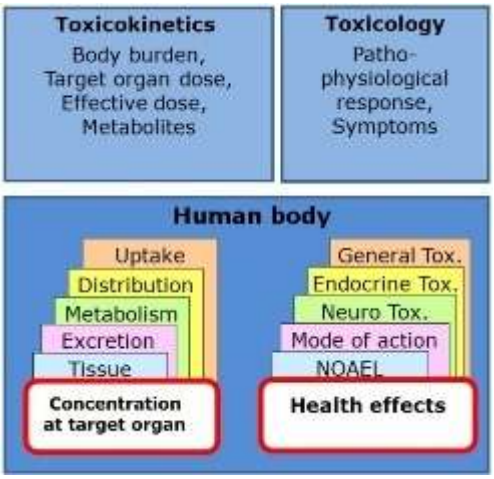
a) Direct contact/dermal?* b) Inhalation?* c) Ingestion?

9. What is your level of confidence in the scientists' ability to predict the exposure of infants and children to BDE-209 via the following routes:

a) Direct contact/dermal?* b) Inhalation?* c) Intrauterine?*

d) Via food?* e) Via breast milk?*

Toxicokinetics



10. What is your level of confidence in the scientists' ability to predict to what extent BDE-209 is:

a) Absorbed/taken up?*

b) Metabolised to hydroxy-metabolites after absorption?*

c) Debrominated to lower brominated congeners after absorption?

d) Debrominated or metabolised by the intestinal microflora?*

e) Accumulating in the body?*

f) Excreted via bile and faeces?* g) Excreted via urine?*

11. Regarding BDE-209, what is your level of confidence in the scientists' ability to predict

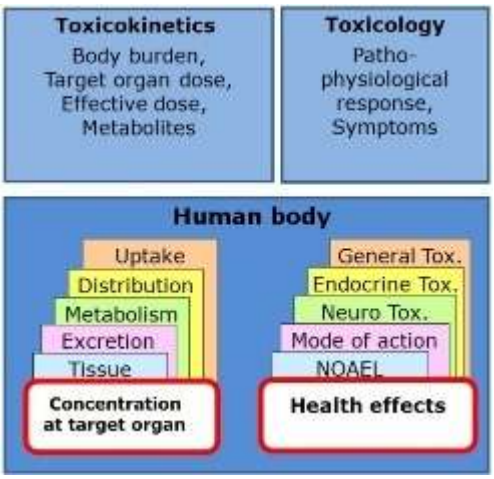
a) The distribution to different tissues?*

b) The final concentration of the parent compound in the target tissues, taking factors such as absorption, distribution, metabolism and excretion into account?*

c) The final concentration of metabolites in the target tissues, taking factors such as absorption, distribution, metabolism and excretion into account?*

d) The biological half-life?*

Toxicology



12. Based on human epidemiological studies, what is your level of confidence in the scientists' ability to predict adverse effects of BDE-209 in

a) Males?* b) Females?*

13. Based on experimental animal studies, what is your level of confidence in the scientists' ability to predict adverse effects of BDE-209 on general health in

a) Males?* b) Females?*

14. Based on experimental animal studies, what is your level of confidence in the scientists' ability to predict adverse effects of BDE-209 on neurodevelopment in

a) Males exposed during foetal or neonatal life?* b) Females exposed during foetal or neonatal life?*

15. Based on experimental animal studies, what is your level of confidence in the scientists' ability to predict adverse effects of BDE-209 on thyroid function in

a) Males exposed as adults?* b) Females exposed as adults?*

c) Males exposed during foetal or neonatal life?*

d) Females exposed during foetal or neonatal life?*

16. Based on experimental animal studies, what is your level of confidence in the scientists' ability to predict adverse effects of BDE-209 on reproductive function in

a) Males exposed as adults?* b) Females exposed as adults?*

c) Males exposed during foetal or neonatal life?*

d) Females exposed during foetal or neonatal life?*

17. Based on experimental studies, what is your level of confidence in the scientists' knowledge of the mechanisms of action of

a) BDE-209?* b) Metabolites of BDE-209?*

18. What is your level of confidence in the scientists' ability to predict the NOAEL of BDE-209?*

Final comments

Finally, do you think that any relevant questions were left out or that any questions were superfluous? Please describe:

STEP 2: DECABDE REVIEW-BASED BACKGROUND INFORMATION

This document is mainly based on recent reviews and reports. Where appropriate, the referred original study is underlined, followed by the review or report in separate brackets. Original studies referred to directly are not underlined.

Both terms decaBDE and BDE-209 occur in the document, it is aimed at using decaBDE for the technical mixture and BDE-209 for the single congener.

Sources

Production and applications

Bromine has flame retarding properties and polybrominated diphenyl ethers have therefore been used for decades in various products to slow down development of fire and thereby save lives and reduce material damage (Frederiksen et al. 2008).

While penta- and octaBDEs were banned in EU in 2004 and followed by 10 states of the USA, decaBDE is still produced and used worldwide (56 100 tons/year in 2001)(Frederiksen et al. 2008). Originally, decaBDE was banned for the use in electrical and electronic applications in the EU together with the other BDEs, but was later exempted from the ban by the Commission. In 2008, the European Court of Justice decided that the Commission had exempted decaBDE on false premises and consequently it was again put a ban to its use in these products (Court of Justice of the European Communities 2008) .

Commercial decaBDE mixtures contain 97% or more BDE-209. The last percentages consist of nonaBDEs and maybe trace amounts of octaBDE (U.S.Environmental Protection Agency 2008).

Materials and goods

Brominated flame retardants have been used in electronics like TVs, computers, mobile phones and in various electrical kitchen appliances. Also upholstery, textiles, building materials and plastic products, as well as cars and airplanes will often contain brominated flame retardants (Frederiksen et al. 2008). DecaBDE is mainly used in textiles and television and computer castings (Costa and Giordano 2007). Approximately ¾ are used in plastics and ¼ in textiles (European Chemicals Bureau et al. 2007).

End of life leakage

Large quantities of brominated flame retardants were found in close proximity to an e-waste recycling site in China, and BDE-209 was the dominating congener in soil and many of the sediment samples. This indicates that electronic devices may contribute to high local environmental levels of BDEs and BDE-209 in particular if not handled appropriately at recycling. A steadily increasing turn-over rate of electronic equipment will be a major contributor to future environmental concentrations (Wong et al. 2007).

Environmental Matrix

BDE-209 makes up a great part of the total PBDE content in air, water and sediments. Relatively recent studies show debromination of deca-BDEs into more toxic and bioaccumulative congeners in abiotic and

biotic processes (Ross et al. 2008), such as photolytic debromination in house dust (Stapleton and Dodder 2008) and in plastics (Kajiwara et al. 2008) by natural sunlight. BDE-209 measured on atmospheric particles collected in remote areas as well as in urban regions, suggests that also this congener are transported long distances through the air (de Wit et al. 2006) (Ross et al. 2008). This is also evidenced by its presence in arctic food webs and its relatively high contribution to the total PBDE concentration in some arctic animals (Jenssen et al. 2007).

Sediment

Sediment cores show an historical build-up of the congener. This makes a great reservoir of BDE-209 in sediments which may pose a risk to lower trophic levels while upper trophic levels are more prone to be affected by their potential breakdown products (Ross et al. 2008). BDE-209 accounts for around 80% of the total PBDE in Strait of Georgia sediments (Ross et al. 2008). In European sea water sediments three studies of 10-13 samples have revealed BDE-209 concentrations of 0.03µg/kg dry weight (German Bight 2002-2005) to 132µg/kg dry weight (Spanish coast) (Law et al. 2008). In Belgium, BDE-209 content in the layers of two sediment cores was determined to be in the range of 315 to 8410µg/kg dry weight (Covaci et al. 2005) (Law et al. 2008). Also in European river sediments, BDE-209 constitutes the greatest part of the total BDEs and accounts for approximately 50-60% (Law et al. 2008). So it does in Asian coastal and river sediments, where the highest concentrations are found in Chinese Pearl River (up to 3580µg/kg dry weight) (Mai et al 2005), while 2248µg/kg dry weight was the upper range of what was measured in Korean costal surface sediments (Moon et al. 2007). Besides, levels of BDE-209 still increase in sediments of Tokyo Bay while the other BDEs show a decreasing trend (Minh et al. 2007) (Law et al. 2008).

Sewage sludge

BDE-209 seems to dominate the congener profile in sewage sludge. In altogether 5 studies from 4 European countries sewage sludge samples from 8 to 50 different plants showed concentrations of BDE-209 ranging from approximately 10µg/kg dry weight (Czech Republic) to 4150µg/kg dry weight (Spain) (Law et al. 2008).

BDE-209 has shown to have a half-life of 700 days under anaerobic conditions in sewage sludge (Gerecke et al. 2006). One study showed no evidence of debromination during the process in wastewater plants (Knoth et al. 2007) (Law et al. 2008).

Soil

BDE-209 was the dominating congener in all soil samples collected from 5 sites in Sweden in 2000, with concentrations of 0.015µg/kg dry weight (reference site) to 3900µg/kg dry weight (sewage sludge amended site). Time since sludge amending in relation to the concentrations measured indicated high persistence of this congener in soil/sludge. No photolytic debromination was seen (Sellström et al. 2005) (Law et al. 2008). The same concentrations were observed at the reference site in a Spanish study (14.6ng/g dry weight), but lower on the amended sites (up to 1082 ng/g dry weight) (Eljarrat et al. 2008).

Water

Discharge of BDE-209 to aquatic systems and coastal oceans is exponentially increasing (Ross et al. 2008). Few studies have measured concentrations of BDEs in water because their hydrophobicity will make them absorb to particulate matter. However, in a study where dissolved and suspended phases of sea-surface micro layer and sea water in Hong Kong were measured, BDE-209 was not measured in concentrations above detection limit in any samples, while BDE-28, BDE-47 and BDE-100 were the dominating congeners (Wurl et al. 2006) (Law et al. 2008).

Dust

BDE-209 is the most abundant of the measured PBDEs in house dust (32-97%). The levels of BDE-209 is higher in North America (630-2000ng/g dw, 6 studies, n between 5 and 64) than in Europe (60-466ng/g dw in continental Europe and Scandinavia 5 studies of n from 1 to 10, 7100 ng/g dw measured in UK, n=10, one study) (Frederiksen et al. 2008). Other measurements from the UK have also revealed high concentrations of the BDE-209 (two samples 520 000 and 100 000 µg/kg, median 2800 µg/kg (Harrad et al. 2007) (Law et al. 2008). In Kuwait, levels of PBDEs in dust were lower than in Europe (83ng/g dw, n=17), but BDE-209 accounted for nearly 90 %, while Singapore levels from dust in air conditioners levelled the North American levels (2200 ng/g dust weight, n=31) (Frederiksen et al. 2008).

Air

The type of sample collector may influence the result. On one hand passive samplers primarily sample the gas phase and therefore may underestimate concentrations of the higher molecular weight BDEs, while on the other hand some active samplers which sample the particulate phase will underestimate small molecular weight BDEs. Methods of dust sampling also vary (Law et al. 2008). Unlike other congeners, BDE-209 is not evenly distributed between gas and particulate phase; it is present almost exclusively in the particle phase (Venier and Hites 2008).

Indoor air

Homes

BDE-209 is suggested as the main congener in indoor air (median 64-173pg/m^3) in five studies conducted in Europe and North America with between 4 and 73 samples collected in each study (Frederiksen et al. 2008). BDE-209 was measured and found to be the dominant PBDE congener in car-air (Greece:104pg/m^3) (Mandalakis et al. 2008) and concentration of PBDEs were higher in newer cars (Frederiksen et al. 2008).

Occupational

High levels of BDE-209 are found in electronic dismantler halls in Sweden (median 15 340pg/m^3 in air incl particles, n=4 and 30 000 pg/m^3 in “personal air”, n=11). BDE-209 was dominating the overall PBDE profile (Frederiksen et al. 2008).

Outdoor air

Levels are lower in outdoor air, but BDE-209 is still among the important congeners (Frederiksen et al. 2008; Law et al. 2008). Atmospheric concentration was measured near Lake Maggiore in Northern Italy

in March 2005 using a high volume sampler. BDE-209 was only present in particulate phase with a concentration of 4.79 pg/m^3 and it was the third most abundant congener measured (Mariani et al. 2008). In Turkey, atmospheric BDE-209 concentrations were measured at one suburban, two urban and one industrial site. BDE-209 dominated the total PBDE profile at all sites. A modified high volume-sampler was used to sample the 60 samples at each of the sites during summer and winter months. Total concentration (gas and particulate phase) of BDE-209 was in the range of 19 (suburban) to 54 (industrial) pg/m^3 in summer and in the range of 10.9 (suburban) to 32.5 (industrial) pg/m^3 in winter. On average the proportion of BDE-209 was 70 +/- 22% at the four sites (Cetin and Odabasi 2008).

Exposure

Dermal

Dermal absorption might happen by direct contact with textiles, furniture, electrical equipment or house dust. Some studies regard this as an important contributor to the overall exposure (Frederiksen et al. 2008). Dermal contact with indoor house dust was calculated to account for 16% of the total body burden of PBDEs in adults (Lorber 2008) (Frederiksen et al. 2008).

Inhalation

Particles or compounds in the gaseous phase or particles will be inhaled and ingested via mucus (Frederiksen et al. 2008). This is probably an important source, however, little is known about how much this contributes to the overall exposure. BDE-209 is the most abundant congener in air, and constitutes up to 62% of total amount of PBDE (Karlsson et al. 2007) (Frederiksen et al. 2008).

Intrauterine

Little is known to which extent the foetus is exposed *in utero*. In a recent French study, BDE-209 was found only in 50% of the cord serum samples, while it was found in 90% of the maternal serum samples. Measured levels however, were much higher in cord serum (median 27.11, range 3.43-363.33ng/g lw, n=36) compared to the maternal serum (median 5.78, range 0.79-37.43ng/g lw, n=64). The reason for this was suggested to be the lower lipid content in cord serum. The median relative contribution of decaBDE in cord serum was 77% to the total levels of octa-, nona- and deca-BDE (Antignac et al. 2009). A Spanish study measured BDE-209 concentrations in cord serum to be 1.4-2.2ng/g lw (median at two different hospitals in Madrid, n=53 and 44, respectively), while it was the predominant congener in placenta (1.0ng/g lw, n= 30) (Gomara et al. 2007). High levels measured in toddlers might be due to breast milk consumption and higher exposure to dust than adults (U.S.Environmental Protection Agency 2008).

Ingestional

Mother's milk

Levels of BDE-209 have shown to be constant from 1987 until 1999 in samples from Faeroe Islands (Frederiksen et al. 2008)

BDE-209 was detected in low concentrations in all samples of mother's milk sampled during 2000-2002 from 10 primipara mothers living in Northern Norway (Polder et al. 2008b). In a French study published in 2009, BDE-209 was found in all 62 analysed breast milk samples from 20 to 46 years old women,

mean 32.5, (range 0.39-6.80ng/g lw, median 1.62ng/g lw) and it was the dominating of the higher brominated congeners (relative contribution of 45% to total octa- to decaBDE concentration) (Antignac et al. 2009). In breast milk from two different areas of Madrid, Spain, sampled three weeks after delivery, BDE-209 was the most abundant congener (2.9ng/g lw, n=22 and 2.8ng/g lw, n=30) (Gomara et al. 2007). Mother's milk from North America has shown mean concentrations of 0.8 (first time mothers, after 8 weeks nursing) and 0.9ng/g lw (20-41 years old) in two different studies with n of 40 and 47, respectively (She et al. 2007, Schecter et al. 2003) (U.S.Environmental Protection Agency 2008). Samples collected from 19 primiparous mothers living in an urban or a rural area of Eastern China contained higher concentrations of BDE-209 than of the other congeners (median: 2.6ng/g lw, all samples), but was only detected in 50% of the samples (Sudaryanto et al. 2008).

Food

Seafood is an important source of BDE-209, especially fatty fish and fish livers. However, meat, eggs and dairy products seem to be a relatively more important source of BDE-209 than of the other PBDEs, probably because of the short half-life of BDE-209; terrestrial animals live closer to the sources than fish do (Ohta et al. 2002) (Frederiksen et al. 2008). Levels of BDE-209 in cod liver and herring from Danish waters have been as high as 50000-60000 pg/g ww, while the general trend is that BDE-209 accounts for less than 10% of the total PBDE content in fish. Much larger fractions are measured in shellfish from Korea and the Netherlands (Frederiksen et al. 2008).

Strong correlation was seen between consumption of fish from a contaminated lake and serum levels of PBDEs. This was not the case for BDE-209, suggesting that other sources than dietary fish are important (Thomsen et al. 2008). Another study indicated that milk products could contribute considerably to the BDE-209 intake (Knutsen et al. 2008). Although levels of PBDEs in vegetables are generally low, spinach has shown to contain large amounts, though BDE-209 was not measured in that study (Frederiksen et al. 2008).

Egg content of BDE-209: 10pg g/ww, n=1, 2003/04, USA

Meat: 38 pg g/ww, n=18, 2003/04, USA

Meat: below detection limit, n= 4-26, 2005, Belgium

Chicken breast: 48pg/g ww, n=1, 2003/04, USA

Cheese: below detection limit, n=3, 2005, Belgium

Milk products: 9.1pg/g ww, n=15, 2003/04, USA

Dairy products: 4.42pg/g ww, n=18, 2003-05, Spain

Oils: 24pg/g ww , n=16, 2003-05, Spain

Infant formula: 14pg/g ww, n=1, 2003/04, USA

(Various authors)(Frederiksen et al. 2008)

Dust

Dust is an important source of BDE-209. Dust in gaseous and particulate phase is inhaled and ingested with mucus (Frederiksen et al. 2008). Dust is regarded the most important source of BDE-209 exposure for many people in the UK and can be inhaled and then ingested as well as absorbed through skin via direct contact, while penta-BDE mixtures mainly are ingested via food (Law et al. 2008). BDE-209 is the most abundant of the measured PBDEs in house dust (32-97%). The levels of BDE-209 is higher in North America (630-2000ng/g dw, 6 studies, n between 5 and 64) than in Europe (60-466ng/g dw in continental Europe and Scandinavia 5 studies of n from 1 to 10, 7100 ng/g dw measured in UK, n=10, one study) (Frederiksen et al. 2008). Other measurements from the UK have also revealed high concentrations of the BDE-209 (two samples 520 000 and 100 000 µg/kg, median 2800 µg/kg (Harrad et al. 2007) (Law et al. 2008). In Kuwait, levels of PBDEs in dust were lower than in Europe (83ng/g dw, n=17), but BDE-209 accounted for nearly 90 %, while Singapore levels from dust in air conditioners levelled the North American levels (2200 ng/g dust weight, n=31) (Frederiksen et al. 2008).

Human body

Toxicokinetics

Uptake

There are no direct quantitative studies on BDE-209 absorption in humans; however, measured concentrations in humans indicate absorption (U.S.Environmental Protection Agency 2008). For example, uptake from air/air particulates may happen through inhalation of particulates followed by swallowing or direct dermal contact and is indicated by clear evidence of occupational exposure. It is shown to be taken up in animals of the aquatic food web, but at lower levels than other congeners. Its uptake is probably hindered by particle binding (Ross et al. 2008). However, BDE-209 is demonstrated to bioaccumulate in terrestrial food chains and mammal predators, and it may be more important for birds feeding in terrestrial, than in marine habitats (Law et al. 2008). Though also in mammals (rodents) absorption of decaBDE is much lower than for lower brominated congeners (Morck et al. 2003)(Costa and Giordano 2007). Absorption range of 7-26% is indicated for rats; however, accurate measurements are difficult because of the high content of the compound and metabolites in faeces. It is indicated that absorbed and metabolised decaBDE accounted for around 10% of the faecal excretion (U.S.Environmental Protection Agency 2008). Very small amount has been shown to be absorbed through mice skin in vitro. Only 0.07-0.34% had passed through the skin sections 24 hrs after they were exposed to 6, 30, and 60nmol in a flow through diffusion system and the percentages passed were inversely related to dose (Hughes et al.2001) (U.S.Environmental Protection Agency 2008).

Distribution

BDE-209 distributes differently from the other highly brominated congeners, which are found in the highest concentrations in adipose tissue (Morck et al 2003) (Costa and Giordano 2007). Hydrophilic metabolites, molecular mass and favoured conformation may be factors leading to a low uptake by adipocytes (U.S.Environmental Protection Agency 2008). Most available knowledge on distribution in humans originates from monitoring of levels in human populations. Thus, data is scarce and mostly limited to milk and blood. BDE-209 is distributed and secreted in human milk but is found at low levels compared to other congeners (U.S.Environmental Protection Agency 2008; Polder et al. 2008a). In blood however, BDE-209 seems to reach higher levels, and levels in an infant and a toddler showed to be

unusually high compared to their parents (U.S.Environmental Protection Agency 2008). In French mothers, levels of BDE-209 were found to be highest in cord serum (where the compound was found, median 27.11ng/g lw), followed by lower levels in maternal serum (median 5.78ng/g lw), milk (median 1.62ng/g lw) and adipose tissue (median 0.75ng/g lw) (Antignac et al. 2009).

Metabolites were found in both maternal and foetal tissues after exposure of pregnant rats to BDE-209. Thus the metabolites can pass placenta and enter the foetus (Riu et al. 2008) (Legler 2008). The congener has also shown to dominate the PBDE profile in human placentas (1.0ng/g lw, n=30) in a Spanish study (Gomara et al. 2007). Presence of BDE-209 has been detected in mouse neonatal brain and heart (Viberg et al. 2003) (Legler 2008). The compound was also detected in all tissues examined in rats 3-7 days after oral exposure to 2.9mg/kg 14C-labelled and unlabelled decaBDE: liver, adipose tissue, lung, kidney, adrenal glands, skin, muscle, spleen, testis, thymus, heart, plasma and colon wall and small intestine wall. Levels measured indicated distribution to blood rich tissues rather than to lipid-rich tissues (Morck et al. 2003) (U.S.Environmental Protection Agency 2008). In more studies, highest concentrations were measured in liver and plasma, though overall the relative distribution to different tissues varies across studies in adult rodents. Age-dependent differences in distribution to liver and developing brain have also been revealed (U.S.Environmental Protection Agency 2008).

Human tissue levels

Blood

In 21 pooled serum samples from the general Norwegian population, BDE-209 were detected in all samples, however, they did not show the same time trends as the other congeners, which rose until late 1990's and then stabilised. This might be due to the shorter half-life of BDE-209 (Thomsen et al. 2007) (Law et al. 2008). In Japan, 89 mothers had a range of 0.74-21.19 ng/g lipid sum of PBDEs in their blood and the most prominent congener was BDE-209 (Inoue et al. 2006) (Costa and Giordano 2007). In 64 analysed serum samples of mothers collected in France, the concentration range was 0.79ng/g lw-37.43ng/ g lw and the median value was 5.78ng/g lw (Antignac et al. 2009).

7 year old children had a higher blood level of BDE-209 than their mothers (Frederiksen et al. 2008). In one Californian family, the breast fed infant serum concentration of BDE-209 reached 233ng/g lw, in the 5 –year old sister 143ng/g lw, while the mother and father had serum concentrations of 14 and 23ng/g lw, respectively (Fischer et al. 2006) (U.S. Environmental Protection Agency, 2008). High concentrations were also measured in occupationally exposed individuals in Sweden (up to 34ng/g lw) and China (86 and 310ng/g lw) (Frederiksen et al. 2008).

Milk

Other PBDEs are dominating in human milk samples, while levels of BDE-209 were found to be low as seen in Northern Norway (median 0.13ng/g lw)(Polder et al. 2008b), North western Russia (median 0.19ng/g lw, n=37) (Polder et al. 2008a), France (median 1.62ng/g lw) (Antignac et al. 2009), in the Pacific Northwest of the U.S. and British Columbia (median 0.4ng/g lw) (She et al. 2007) and in U.S. mothers with various ethnical backgrounds (mean 0.9ng/g lw) (Schecter et al. 2003) (U.S.Environmental Protection Agency, 2008). In Eastern China median concentration was found to be 2.6ng/g lw, but BDE-209 was only detected in 50% of the samples (Sudaryanto et al. 2008).

Adipose Tissue

Adipose tissue levels in samples collected during caesarean sections could be quantified in 79 of the 86 samples collected. Concentration ranged from 0.13 to 4.39ng/g lw and the median value was 0.75ng/g lw. This was lower than in milk, maternal serum and in cord serum which were sampled in the same study (Antignac et al. 2009). In Japan, median concentration of BDE-209 in adipose tissue from 28 donors (18 males and 10 females) collected at autopsy during 2003-04, was 1.2 ng/g lw (range: <0.5-12) in males and 0.74 ng/g lw (range: <0.5-1.7) in females (Kunisue et al. 2007).

Metabolism

Data regarding metabolic processes in humans is difficult to achieve.

BDE-209 is readily metabolised in rodent tissues (U.S.Environmental Protection Agency 2008). While the other PBDE congeners are metabolised to mono- or di-hydroxylated metabolites, BDE-209 is both metabolised to hydroxylated metabolites and debrominated to other congeners, such as the more accumulating and toxic nona-, octa-, and heptaBDEs (Morck et al. 2003; Huwe and Smith, 2007) (Costa and Giordano 2007). Reductive debromination is suggested to be the first step in the metabolic pathway followed by oxidation to phenolic metabolites. Some debromination may happen through the activity of the CYP1A1 and CYP2B1 enzymes (Zhou et al. 2001) (U.S.Environmental Protection Agency 2008). Metabolism may occur both in liver and in epithelium of the gastrointestinal tract or by the intestinal micro flora. After i.v. injection of decaBDE in rats 63% of the fecal BDE-209 content was metabolised, while 37% was intact BDE-209 (el Dareer et al. 1987) (U.S.Environmental Protection Agency 2008). In a 21-days dietary exposure study in rats, hepta- to nonaBDEs constituted 1.5% of the dose of decaBDE mixture, whereas they accounted for 16-22% of the total PBDE concentration measured in the tissues. Some of these lower brominated congeners showed a much higher propensity to bioconcentrate than BDE-209 (Huwe and Smith 2007). Evidences of *in vivo* debromination are also observed in starlings (van den Steen et al. 2007), fish and fish liver microsomes (Stapleton et al. 2006).

Excretion

BDE-209 appears to be excreted more rapidly than the other congeners. The half-life in humans is days to months for octa- to decaBDEs in contrast to the lower brominated congeners which half-lives are in the order of years (Costa and Giordano 2007). Thuresson et al. 2006 estimated the half-life of BDE-209 in humans to be 15 days. Shorter and longer half-lives have been found in rats; after oral and intravenous injection of one single dose of decaBDE using a three-compartment model, the half-life was estimated to be around in total 2.5 days (Sandholm et al. 2003) (U.S.Environmental Protection Agency 2008), while repetitive oral dosing for 21 days led to a half-life of 75 days in rats (Huwe and Smith 2007) (Costa and Giordano 2007). When all metabolites are taken into account, the half-life is expected to be prolonged (U.S.Environmental Protection Agency 2008). Main route of excretion in rodents is through faeces, while urinary excretion seems to be of minor importance (less than 1%). After oral exposure most BDE-209 (around 90%) is excreted unabsorbed in faeces. Biliary excretion accounts for approximately 10% of the amount measured in faeces. Most (around ¾) of the dose will be excreted within 72 hours regardless the administration method, and most of this during the first 24 hours (U.S.Environmental Protection Agency 2008).

Toxicology

General toxicity

DecaBDE is less potent than the other BDEs. Knowledge on general toxicity is obtained through animal experiments. The observations suggest that males are more sensitive than females (NTP, 1986) (U.S.Environmental Protection Agency 2008)

Short term studies (up to 14 days) in adult rodents did not reveal any effects on the endpoints examined at the applied oral doses of decaBDE of 97-99% purity (up to 20 994mg/kg/day in males and 23 077mg/kg/day in females) (U.S.Environmental Protection Agency 2008).

In oral exposure studies of longer duration (decaBDE with 94-97% purity for two years, starting from 7-8 weeks of age), the following was observed:

Male rats exposed to 0, 1120 or 2240mg/kg/day: significant increased incidence of liver thrombosis, liver degeneration, fibrosis of the spleen, lymphoid hyperplasia in the mandibular lymph node in the high dose group and increased incidence of neoplastic nodules in the liver in both low- and high-dose groups

Female rats exposed to 0, 1200 or 2550mg/kg/day: the only significant finding was increased incidence of neoplastic nodules in the liver in the high dose group

Male mice exposed to 0, 3760 or 7789mg/kg/day: significant increased incidence of centrilobular hypertrophy in the liver and follicular cell hyperplasia in thyroid gland in the high- and low-dose group

Female mice exposed to 0, 3760 or 7780mg/kg/day: statistically significant increase in the incidence of stomach ulcers in the high dose-group.

Genotoxicity

Despite the observed increased incidences of neoplastic nodules in rats, decaBDE has shown not to be genotoxic. No chromosomal aberrations or sister-chromatid exchanges were observed in Chinese hamster ovary cells exposed to doses of up to 500µg/ml in presence and absence of an exogenous metabolic system. Parent decaBDE in the presence or absence of exogenous metabolic system did not exert mutagenic properties either when tested in vitro on *Salmonella typhimurium* strains (up to 10 000µg/ml) or in a mouse lymphoma cell assay system (up to 10µg/ml) (NTP, 1986) (U.S.Environmental Protection Agency 2008). Increase in reactive oxygen species were found in human hepatoma cells after exposure to 10-100µM BDE-209 (Hu et al. 2007) (Costa and Giordano 2007).

Neurotoxicity

Neurobehavioral effects have been reported after exposure to single and repetitive doses during critical windows of development in rodents. PBDEs are reported to interfere with thyroxin levels and this might contribute to behavioural changes as these hormones play a crucial role in brain development (Costa and Giordano 2007). Also neurodevelopmental toxicity studies indicate that males may be more sensitive to decaBDE than females, although females have not been studied to the same extent as males.

When the animals are exposed during development, much smaller doses over shorter periods, even single doses may cause effects. Time of exposure has been shown to be of great importance for development of adverse neurological effects. A Swedish research group has performed several behavioural studies in rats and mice, where the endpoints rearing, locomotion and total activity in rodents exposed neonatally (decaBDE, >98-99% purity, in 20% fat emulsion, oral gavage) were assessed in three successive 20-minute periods months after exposure. The following findings are published:

Post natal day (PND) 10 was suggested to be a sensitive window in rat and mouse brain development. However, exposure to decaBDE only caused effects when the animals were exposed prior to this, on PND 3, probably due to the slow accumulation in the brain of this congener or its metabolites. Interestingly, no effects were seen when exposure took place at PND10 or 19, and when exposed on PND 19 also brain accumulation of BDE-209 was lower (Viberg et al. 2003) (Costa and Giordano 2007).

Male mice treated with 20.1 mg/kg/bw decaBDE on PND 3 showed abnormal habituation; reduced activity for locomotion, rearing and total activity compared to controls the first 20-minute period and hyperactivity the third 20-minute period of the test at 2, 4 and 6 months of age (Viberg et al. 2003) (U.S.Environmental Protection Agency 2008).

Male mice exposed to 2.22mg/kg decaBDE on PND 3 only showed minor changes in behaviour when subjected to the same tests as the 20.1mg/kg exposed mice (Viberg et al. 2003) (U.S.Environmental Protection Agency 2008).

Male rats exposed to 20.1mg/kg decaBDE on PND 3 showed similar pattern in behaviour as the 20.1mg/kg treated mice at 2 months of age. The test was not carried out at 4 or 6 months (Viberg et al. 2007) (U.S.Environmental Protection Agency 2008)

Male rats exposed to 6.7mg/kg decaBDE on PND 3 showed increased locomotion and decreased rearing during the second 20-minute period and increased total activity during the first and second 20 minute periods at 2 months of age (Viberg et al. 2007) (U.S.Environmental Protection Agency 2008).

Decreased activity in 20.1mg/kg exposed rats treated with nicotine compared to 20.1mg/kg exposed rats injected with saline, suggested that BDE-209 might interfere with the cholinergic system (Viberg et al 2007) (U.S.Environmental Protection Agency 2008)

Male mice exposed to doses of 1.34, 2.22, 13.4 and 20.1 mg decaBDE /kg bodyweight on PND 3 displayed a dose-related change in all three test variables; locomotion, rearing and total activity at two and four months of age. The test was not carried out at 6 months of age (Johansson et al. 2008).

Male mice given 2.22 to 20.1mg/kg/ bw decaBDE were less active than controls and mice in the lowest exposure group during first 20 minutes at 2 and 4 months of age (Johansson et al. 2008).

13.4 and 20.1 mg/kg (also 2.22 at four months) exposure groups of male mice were significantly more active during the last 20-minute period at 2 and 4 months of age (Johansson et al. 2008).

Also in this study, the nicotine- injected animals of the two higher dose-groups showed less activity than the saline injected during the 20 first minutes, in contrast to the control group and lower dose groups, and higher activity than controls during the last 20 test minutes (Johansson et al. 2008).

Another research group has also studied effects on neurodevelopment in mice:

In mice of both sexes exposed orally to 6 and 20mg/kg decaBDE (99.5% purity in 20% fat emulsion, administered by a micropipette) during post natal days 2-15, it was observed a delay in palpebral reflex on PND 14 and the 6mg/kg-group struggled more during handling than controls on PND 20 (Rice et al. 2007) (Costa and Giordano 2007).

Male 20mg/kg/ day group did not perform an effective forelimb grip on PNDs 14 and 16 (Rice et al. 2007) (Costa and Giordano 2007).

Locomotor activity in a new environment declined over a 2 hrs period in all animals in the same study on PND 70, however, both exposure groups of males showed less decline than control, while females showed hypoactivity compared to controls. These effects were no longer seen when the mice were one year old (Rice et al. 2007) (Costa and Giordano 2007).

Experiments with killifish, also showed hypo-and hyperactivity depending on dose, when the fish were exposed during embryonic stage (Timme-Laragy et al. 2006) (Costa and Giordano 2007).

Endocrine toxicity

Observations from studies on endocrine system include interference of decaBDE with the thyroid hormones, some effects on male reproduction and altered expression of genes important for hormonal homeostasis. Knowledge on endocrine toxicity is obtained from animal experiments.

In female Wistar rats exposed to decaBDE for 28 days increased levels of circulating triiodothyronine were observed after exposure to a high dose (van der Ven et al. 2007) (Legler 2008). Oral exposure of mice to a dose of 6 and 20mg/kg on postnatal day 2-15 decreased levels of plasma T_4 in males in a dose-related fashion on PND 21 (Rice et al 2007) (U.S. Environmental Protection Agency, 2008).

No expression of an oestrogen receptor-mediated luciferase reporter construct was seen after exposure of zebra fish to different BDEs among them BDE-209, through food and water (Legler et al. 2005) (Legler 2008). Oral exposure of rats to decaBDE (>97% purity, phospholipon emulsion) for 28 days caused increased male accessory reproductive organ sizes at a bench mark dose level of 0.2mg/kg bw/day, as well as increased hepatic expression of CYP1A and CYP2B (BMDL 0.5-0.7mg/kg bw/day) and decreased expression of the steroidogenic enzyme CYP 17 in female adrenals (BMDL 0.18mg/kg bw/day) (van der Ven et al. 2008). Doses of 10-1500mg/kg/day (oral gavage, 98% purity in corn oil) from PND 21-70 did not affect sperm count or function in mice, but there were indications of sperm oxidative stress and a decrease in amplitude of lateral head displacement and decreased number of sperm with high mitochondrial membrane potential in the 500 and 1500mg/kg/day exposed mice (Tseng et al. 2006) (U.S.Environmental Protection Agency 2008).

In 2002, few effects were observed in a developmental toxicity study where mated females were administered decaBDE of 97.34% purity in corn oil by oral gavage during gestation days 0 through 19. Doses applied were 0, 100, 300 and 1000 mg/kg/day and dams were sacrificed at GD 20. A statistically significant increase in food consumption up to day 12 of gestation and in the mean number of early resorptions per dam were observed in the high dose group, but neither of these findings were considered toxicologically significant (Hardy et al. 2002) (U.S.Environmental Protection Agency 2008).

Mode of action

DecaBDE may act via different modes of action. Different endpoints have been studied.

Mice exposed orally to 20.1mg/kg decaBDE on post-natal day 3 showed decreased levels of autophosphorylated-active alpha Ca^{2+}/calmodulin-dependent protein kinase II, brain derived neurotrophic factor and Gap-43 (neuromodulin) which were investigated for being possible contributors to the observed neurodevelopmental effects in the same animals. Also, the rats exposed to 20.1 and 13.4mg/kg were hypoactive when injected with nicotine compared to control animals and those exposed to lower doses. This indicates interference of BDE-209 with the cholinergic system when the animal is exposed during brain development (Viberg et al. 2007) (Costa and Giordano 2007; Johansson et al. 2008).

4 days of 100mg/kg/day exposure of weanling rats did neither reveal change in thyroid hormone levels, nor in activity of hepatic enzymes which could affect thyroxin homeostasis (Zhou et al. 2001) (U.S.Environmental Protection Agency 2008).

There is evidence that BDE-209 may affect steroid hormone homeostasis as it has induced expression of steroid metabolising CYP-enzymes (cyp3a11 and 2b10, but not cyp1a1/2) (Pacyniak et al.2007) (Legler 2008) in mice. In a recent study, hepatic expression of CYP1A mRNA in rats of both sexes and CYP2B mRNA in males and their respective enzyme activities were increased (BMDL 0.5-0.7mg/kg bw/day) and expression of the steroidogenic enzyme CYP 17 in female adrenals decreased (BMDL 0.18mg/kg bw/day) (van der Ven et al. 2008). DecaBDE have earlier shown not to activate Ah receptor, but have appeared to be a very weak oestrogen receptor antagonist, which is most likely of no biological significance (U.S.Environmental Protection Agency 2008). It has also shown to activate receptors (PXR, dose dependent up-regulation, doses 0.1-100 µM and SXR, only at 100 µM) related to expression of the induced CYP enzymes in vitro (Pacyniak et al. 2007)(Legler 2008).

NOAEL

EPA 2008 report on decaBDE uses the NOAEL from Viberg et al. (2003), 2.22mg/kg as a point of departure for estimating the oral reference dose (RfD). The LOAEL in this study, 20.1mg/kg administered orally on PND 3 to mice gave effects on locomotion, rearing and total activity at 2, 4 and 6 months of age (U.S.Environmental Protection Agency 2008). Two other studies also revealed the neurobehavioral effects to the same dose and lower doses (around 6mg/kg) in rats and mice dosed at the same PND (Viberg et al. 2007) or during the same period of life (PND2-15) (Rice et al. 2007). These two studies did not identify a NOAEL as effects were seen in the lowest dose groups. None of the three studies included more than two exposure groups. The study design in the Viberg et al. (2003) study has been criticized. 10 mice were randomly selected from three to five litters in each treatment group. EPA discusses this as a potential introduction of litter effect and biased results. EPA also mentions that more neurobehavioral endpoints could have been included and that only males were studied. The effects revealed by the Rice et al. (2007) study support and strengthen the evidences, as other neurobehavioral endpoints, and mice of both sexes were included. EPA states that the effects seen only after a single dose given in the Viberg et al. (2003) study increases the concern of the observed effects. This study also suggests PND 3 to be a critical window in brain development. These factors in addition to the supporting evidence from other studies were important in EPA's decision to use this as a point of departure for calculating the oral reference dose. The RfD was calculated to be 7µg/kg/day, when the following uncertainty factors were

used: extrapolating animal data to humans (10), susceptible human subpopulation (10) and extrapolating from a single-dose to a life-time exposure (3) (U.S.Environmental Protection Agency 2008).

A new experiment conducted in 2008 by the Viberg group suggests effects at lower doses for the same neurobehavioral endpoints (Johansson et al. 2008).

Based on two studies in rodents, EPA has estimated the limit for the effective dose (LED12) to be 178 mg/kg/day for the most sensitive endpoints (neoplastic nodule or carcinoma) and used this as the point of departure for calculating cancer oral slope factor; $7*10^{-4}$ per mg/kg/day. The doses associated with excess cancer risk of 10^{-4}, 10^{-5} and 10^{-6} are approximately 100, 10 and 1 µg/kg/day. The estimate is somewhat uncertain as some neoplastic nodules today would be characterized as non-neoplastic hyperplasia and the slope factor assumes that all neoplastic nodules were preneoplastic cellular changes with the potential to become malignant (U.S.Environmental Protection Agency 2008).

STEP 3: RESULTS FROM THE EVALUATION QUESTIONNAIRE FOR DECABDE

PART A - EVALUATION OF THE STRUCTURE AND COMPLETENESS

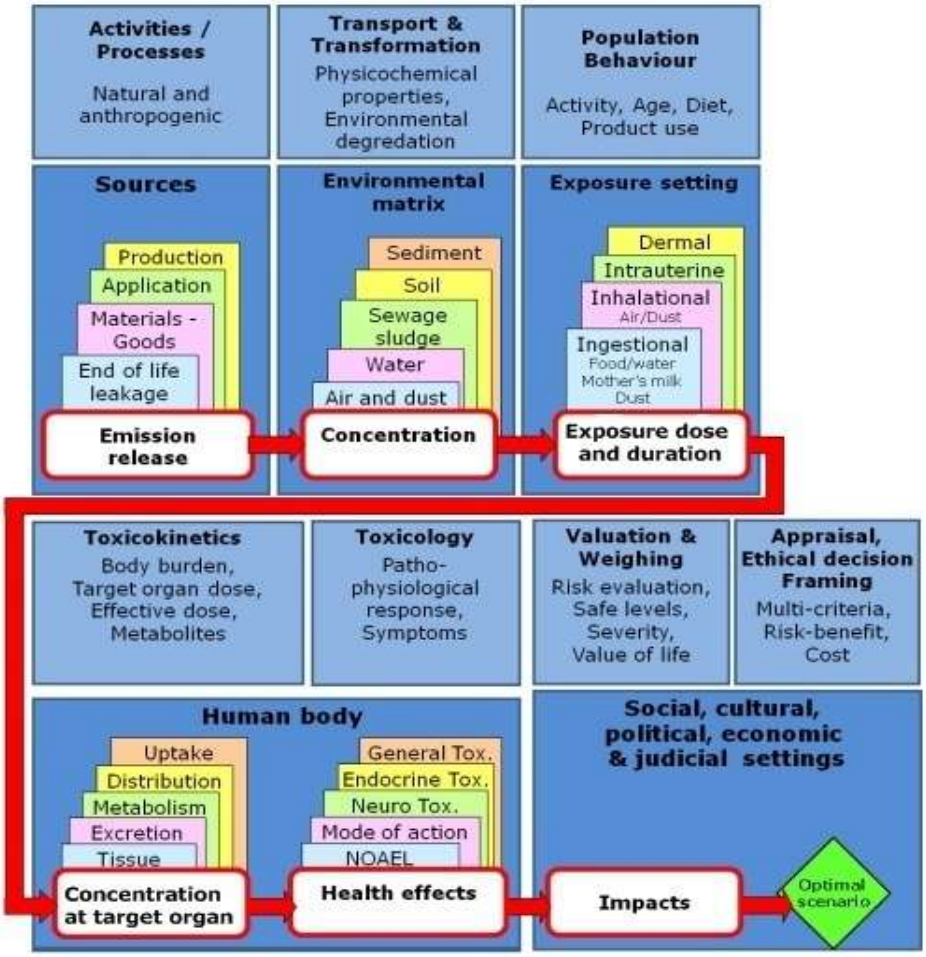


Figure 2: Causal diagram for decaBDE.

Comments to the structure of the causal diagram for decaBDE

Does the diagram take into account all of the important parameters when evaluating the risks related to production?

15 out of in total 23 evaluators answered no to this question and gave a comment to what was missing. The parameter most frequently pointed to was biota, which should be included in the environmental matrix box according to four evaluators. Food stuffs could also be a separate element in this section. Due to direct contamination during some food processing methods, two evaluators mentioned that food processing in itself should be an element in the diagram. Two evaluators thought that materials and goods also belong to environmental matrices because these are a direct source of exposure, with no release into the environment in between. Another two evaluators stated that environmental

transformation to harmful compounds should be visualized more clearly in the environmental matrix box. In the health effect box, two evaluators put a question mark on the way toxicology was categorized; What about cancer, immunotoxicology and other organs? Also, different impacts on different stages of life are not visualized. One evaluator thought that end of life leakage is not a good word as there is leakage from all elements under "Sources". Also, a question was posed on why sediment, soil and sewage sludge are included if the diagram aims to evaluate the risks for human health and if it is because of occasional dermal contact. Finally, it was commented that temporal trends are not visualized and that certain details are missing.

Are the causal relationships adequately structured?

5 evaluators commented on this. One evaluator was missing a visualization of the relation between biota and sediment, water and soil. Another asked if "value of life" should be placed under "ethical decision framing" and stated that "cost" should be cost-benefit.

Are there any unnecessary parameters shown in the diagram that could be deleted?

There were eight comments on this issue. One stated that water could be deleted from environmental matrix since decaBDE will not be found there. Another wanted air and dust to be considered not important transport matrices due to high photochemical transformation rate. "Tissue" in the toxicokinetic section should be "tissue accumulation" or just "accumulation". Some evaluators wanted to reorganize the toxicology box according to the earlier comments on which organs are important in toxicology, while others wanted NOAEL to be deleted and mode of action to be moved to the upper toxicology box. One found the last box not clear and asked what criteria are used for the ethical decision framing and how the political settings are used to assess the optimal scenario.

Part B - Evaluation of individual causal elements

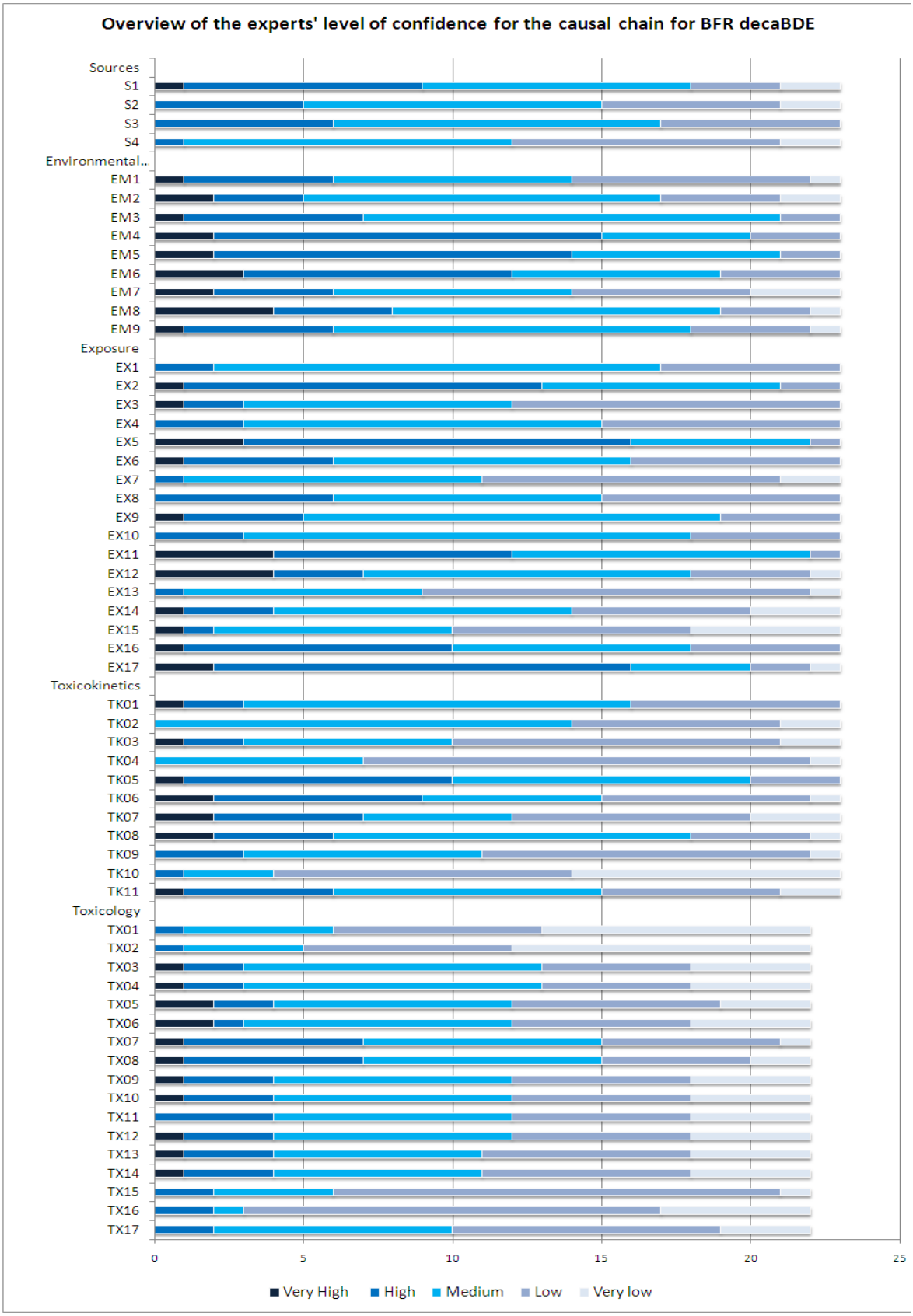


Figure 3: Evaluation results from decaBDE.

Finally, do you think that any relevant questions were left out or that any questions were superfluous? Please describe.

16 of the 23 evaluators gave a comment to this question. Some evaluators said here that they did not feel competent to answer the questions in all fields. Others asked for (more?) questions on debromination in humans and bioavailability. Distribution and lipophilicity were also fields that one evaluator thought should have been addressed. “What is the main route of exposure?” was suggested as an additional question, while another wanted a question on the importance of dust as a source (or other matrices). One evaluator missed a question on the cancer causing ability of decaBDE. The interaction between different types of pollutants is an issue the questionnaire overlooked. The ability of decaBDE to induce liver enzymes responsible for vitamin K metabolism and thereby the potential to pose a risk for hypocoagulability should be put on the agenda according to one evaluator. Certain foods, such as grapefruit, might influence intestinal absorption and metabolite formation of chemicals like decaBDE. This should have been addressed in the questionnaire. One evaluator also thought that the important issue of cord blood levels in relation to the short half-life and time of exposure and sampling would deserve a question.

STEP 4: FOLLOW-UP PRE-WORKSHOP QUESTIONNAIRES

Introduction

Thank you very much for participating in this expert evaluation, conducted in the context of the HENVINET project.

With your help we will further interpret the results of the first evaluation of the state of the art in the scientific knowledge of various aspects of the cause-effect relationship between the production and use of the brominated flame retardant decaBDE and the potential impact on health. You will find the causal diagram on the following page and a summary of the results of the first evaluation following that. The goal of this questionnaire is to identify priorities for further action and to discuss the implications of the results of the evaluation for policy and research. The outcomes of this questionnaire will form the basis for the workshop at the offices of WHO Euro in Copenhagen on May 19th.

In this questionnaire we will first ask you to pinpoint priority elements in the causal diagram. We will then ask you a series of four questions dealing with the implications of the results of the first evaluation on these priority elements. Issues such as research needs and the policy actions justified will be explored.

In the expert workshop on May 19th, a synthesis of the results of the two questionnaires will be presented and discussed in order to arrive at expert advice for EU-policymakers. This advice will be presented during a final stakeholder workshop and discussed in view of enriching the advice with societal viewpoints.

Please return this questionnaire no later than the 11th of May to Hans Keune at hans.keune@ua.ac.be.

We appreciate your participation very much and, on behalf of the the Nowegian Insitute for Veterinary Science, WHO Euro and the HENVINET consortium, we thank you for your time.

WORKSHOP QUESTIONNAIRE

1. In the table below, list the five most important elements of the causal diagram for decaBDE(see annex 1)*. Prioritize according to their influence on the extent of the health risk the causal chain leads to. If a small change in the value of an element results in a large change in the health impact, then this element has a high influence and should be considered very important. Conversely, if a large change in the value of an element leads to only small changes in the health impact, then this element has little influence and is not so important.

You may rank no more then two elements equally; five elements in total.

Priority	Label of element	Please explain why you attribute this priority to this element
1.		
2.		
3.		
4.		
5.		

**If you consider elements that are not represented in the causal diagram to be amongst the five most important, you may include these in the priority list. In Annex 1(after the causal diagram) you will find elements suggested by your colleagues as important supplements to the causal diagram we presented.*

2. Different strengths of evidence justify different policy intervention. For example, a high level of evidence is required to justify banning a substance, while a lower level of evidence might be sufficient to justify initiating a targeted monitoring program or a mandatory labelling scheme.

For each of the priority elements you have identified, indicate the type of action you consider is justified by the evidence available.

Causal elements*	*Conduct Scientific research*					*Policy action* Concrete action by policymakers				Please explain the basis for your choice. If you have any specific scientific studies or hypotheses, please specify them here. If there are any broad implications for science, please explain. If you have any specific policy actions in mind, please specify them here.
	Fundamental science to gain knowledge about the problem			*Applied science* to gain knowledge about solving the problem						
	More data	Better data	Better under-standing	Developing inter-ventions	Experimenting with interventions in practice	Monitor-ing	Awareness raising	Restricting risk activities	Prohibiting risk activities	
1.										
2.										
3.										
4.										
5.										

**As ranked by you in question 1*

Before answering the following questions, please take a moment to consider the "big picture" depicted by the overall results of the first evaluation on decaBDE (provided in annex 2).

With this in mind:

3. What is your level of confidence that conducting more scientific research would yield <u>decisive</u> knowledge on the risks of decaBDE within the next five years? *(decisive knowledge is understood here as knowledge that would clearly dictate which type of policy action is to be undertaken(or not))*

Insert checkmark in appropriate box					Please justify your answer. Also, if you expect decisive knowledge to become available, please specify which of the five causal element(s) you selected in question 1 this knowledge would most likely pertain to.
Very high	High	Medium	Low	Very low	

Interpretive guidance: Very high - At least 9 in 10 chance of being correct; High - At least 7 in 10 chance of being correct;
Medium - At least 5 in 10 chance of being correct; Low - At least 3 in 10 chance of being correct; Very low - 2 in 10 or less chance of being correct

4. What is your level of confidence in the possibility that policy actions to effectively manage the health risks of decaBDE will become technically (not politically) feasible within the next five years? *In other words, are effective policy actions technically feasible now, or to what extent would you expect them to become feasible within the next 5 years?*

Insert checkmark in appropriate box					Please explain why.
Very high	High	Medium	Low	Very low	

Interpretive guidance: Very high - At least 9 in 10 chance of being correct; High - At least 7 in 10 chance of being correct;
Medium - At least 5 in 10 chance of being correct; Low - At least 3 in 10 chance of being correct; Very low - 2 in 10 or less chance of being correct

5. As mentioned above, different strengths of evidence justify different policy intervention.

Considering the overall results of the evaluation, to what extent do you think the current scientific knowledge of the the health risks of decaBDE represents sufficient evidence to justify policy action (or not)?

Insert checkmark in appropriate box

Insufficient evidence to justify a policy intervention	Sufficient evidence to justify <u>not</u> taking policy action	Sufficient evidence to justify a policy intervention

Please explain why you choose this option.

Thank you!!

STEP 5: WORKSHOP REPORT

KEY MESSAGES

Policy context

- Deca-brominated diphenyl ether (decaBDE) is a flame retardant that is widely used in products such as electronics and textiles to impede development of fire and thereby save lives. It belongs to a group of flame retardants called polybrominated diphenyl ethers (PBDEs). The different types (congeners) of PBDEs differ with respect to number and position of bromine atoms in the molecule and decaBDE has the highest possible number of bromines.

- The congeners with lower bromine content have been banned in the EU and some states of the USA due to their environmental persistence, their ability to accumulate in human tissues and the increasing evidence of the ability to cause adverse health effects. DecaBDE is also persistent, but differs from other congeners with respect to some important physicochemical properties: it is less absorbable in human and animal tissues; it accumulates less in these tissues; and it has a lower level of toxicity. On this basis, decaBDE was exempted from the mentioned bans. In 2008, Norway introduced a total ban on decaBDE and EU banned the use of the compound in electronics and electric equipment the same year. A ban on more specific uses, such as mattresses and upholstered furniture is in place in the states of Washington and Maine. More countries propose restrictions on use to be in force within the next few years.

- The main concern with decaBDE is the build-up in and high predominance of this congener compared to lower brominated BDEs found in some environmental compartments such as sediments, soils and dust. The concern relates to data demonstrating that decaBDE, under such circumstances can be broken down to the lower brominated compounds already banned. Microorganisms in the intestines and metabolism in the body are also capable of transforming decaBDE to these lower brominated BDEs or other potentially harmful metabolites. The extent of these processes is a fundamental data gap.

- The relatively high levels in the environment may lead to risk for substantial exposure. In particular, the predominance of decaBDE in house dust may be a major exposure route for small children. Also, toxicological effects observed in animal studies include effects such as disruption of the development of the neurological system and hormonal balance at doses relevant to humans.

- Many electronics companies have already phased out decaBDE voluntarily without specifying which flame retardants they use as substitutes. The main alternatives being proposed for decaBDE are other brominated compounds, phosphorus containing flame retardants and inorganic, non-phosphorus compounds. However, knowledge of the potential risks of these alternatives is also limited.

Policy options

In order to evaluate the state of the current scientific knowledge and highlight important policy considerations, experts were approached by two questionnaires followed by a workshop. Based on the answers from the questionnaires and discussion at the workshop, it was concluded that:

- All experts agreed that more research and monitoring is needed in order to develop a better understanding of the risks involved in the use of decaBDE.
- Experts agreed that three priority areas to investigate are:

  - The extent to which the substance is transformed to compounds with more toxic and tissue accumulating properties in the environment;
  - The extent to which humans and animals are exposed to the compound, especially from food and dust;
  - The extent to which decaBDE is transformed to more harmful substances in the human body.

This is to some extent supported by recent reviews and reports

- Effort should also be invested into research on the toxicity and environmental behaviour of the most frequently proposed alternatives to decaBDE.
- In order to accelerate the rate at which policy relevant information becomes available, experts feel that research collaborations between publically funded institutions should be organised at the European level. In addition to publically funded research, industry should be required to provide more toxicological data.
- There was disagreement among the experts as to whether additional research would yield decisive knowledge on key issues related to decaBDE and its alternatives within five years, given adequate resources. Whereas most were either optimistic or meant that there already is sufficient decisive knowledge available, others stated that research requires more time. Most experts moreover have a medium to high degree of confidence in the possibility that policy actions to effectively manage the health risks of decaBDE are either technically (not necessarily politically) feasible now, or will become so within the next five years.
- While there was disagreement, the majority of experts feel that, in light of the current, all be it limited, knowledge available on the risks of decaBDE, a precautionary ban or restrictions on the use of deca BDE are warranted.

EXECUTIVE SUMMARY

Situation

Brominated flame retardants are used in many different consumer products with the aim of retarding development of fire and thereby save lives and reduce material damage (www.bsef.com). One group of brominated flame retardants is the polybrominated diphenyl ethers (PBDEs). The different types of PBDEs differ with respect to the number and position of bromine atoms in their molecule. DecaBDE, also known as BDE209, has the highest possible number of bromine atoms. The technical mixture of decaBDE contains small amounts of the nonaBDEs, 3% or less (U.S.Environmental Protection Agency 2008). This mixture is almost exclusively used in electrical and electronic equipment, transportation sector, construction and building and textiles (BSEF January, 2009).

Different research and policy communities have different points of view regarding the potential hazards of decaBDE. Penta- and octabrominated diphenyl ethers (penta- and octaBDEs) were found to accumulate in animal and human tissues and to cause harmful health effects, and were banned in the EU in 2004. The primary North American manufacturer voluntarily ceased the production (Vonderheide et al. 2008). The fully brominated BDE congener, decaBDE was regarded less toxic and was eluded from the ban (Vonderheide et al. 2008). In 2008, the European Court of Justice decided that the Commission had exempted decaBDE from the ban on false premises and consequently it was again put a ban to its use in these products (Court of Justice of the European Communities 2008). In Norway, a total ban was introduced in April 2008. Also, the states of Maine and Washington have restricted the use of the substance in certain products, but still many major uses of deca-BDE are allowed in North-America (BSEF January, 2009).

Background

DecaBDE (BDE209) has shown in several studies to be the most abundant PBDE in sediments, sewage sludge, soil, dust and air (Ross et al. 2008; Law et al. 2006). Also, it shows a build-up over years in sediments (Ross et al. 2008) An increasing number of studies show that decaBDE is being transformed into more accumulating, more toxic substances in some environmental matrices in processes involving e.g. microorganisms and sunlight (Ross et al. 2008; Kajiwara et al. 2008). Inhaled and ingested dust is probably the main route of exposure, together with ingestion of food, while direct dermal contact also may play an important role (Frederiksen et al. 2008). The developing foetus and infant will also be exposed through placenta and via mother's milk (Frederiksen et al. 2008; U.S.Environmental Protection Agency 2008). DecaBDE is absorbed from the intestines to a lesser extent than the other BDEs (Costa and Giordano 2007) and when absorbed it is distributed differently. That is, it is measured in relatively higher concentrations in blood and in the liver than in fat tissue which is the primary site of accumulation for the lower brominated compounds (U.S.Environmental Protection Agency 2008). DecaBDE also does not accumulate to the same extent in the body. Animal experiments have shown that decaBDE may be metabolised into more toxic and accumulating BDEs in the gut by microorganisms before absorption, as well as in the liver after absorption (U.S.Environmental Protection Agency 2008). The presence of highly brominated metabolites not found in technical mixtures of BDE in human plasma may indicate debromination also in humans (Antignac et al. 2009), though exposure to environmentally formed metabolites is also a possibility(Stapleton and Dodder 2008). DecaBDE also appears to be excreted more rapidly from the body than the lower brominated BDEs (Costa and Giordano 2007). Subchronic studies in rats have showed toxicological effects only in animals exposed to much higher doses compared to the other PBDEs (Costa and Giordano 2007) . More recent studies have been focussing on exposure to lower doses, closer to the real-life scenario during sensitive time frames of development and observed effects on neurobehavioural endpoints (Johansson et al. 2008; Costa and Giordano 2007) and the thyroxin hormone balance (U.S.Environmental Protection Agency 2008; Legler 2008). There are not many existing effect studies and some are also criticized for their experimental design. The decision by the US Environmental Protection Agency to use one of these studies to set the oral reference dose led to discussions and objections from the industry (Goodman 2009).

To identify knowledge gaps and potential agreement or disagreement on the different aspects of the decaBDE issue a causal diagram illustrating scientists' current understanding of the cause-effect relationship between the production and use of decaBDE and its potential impact on health was made. The diagram was based on the latest review articles and reports available and made similar to more brominated flame retardants. A group of experts was asked to express their confidence in the current knowledge in the different parts of the diagram by completing an online questionnaire. From these experts a group of eight was selected to complete a second questionnaire and take part in an expert panel workshop where the implications of the results of the two different evaluations for policy and health were discussed. Priorities for further action were identified and the workshop aimed at arriving at concrete expert advice for policy makers.

Assessment

Preventing potential adverse effects on human health caused by decaBDE is a task for authorities around the world. Taking appropriate political actions requires sufficient knowledge on the different aspects of chemicals. The required weight of knowledge that is needed to support policy measures with regard to such issues is not well defined though and open for debate amongst experts, policymakers and stakeholders. Both monitoring, modelling, epidemiological and experimental research are, however, quite resource intensive with regards to time and money. Therefore, the most important issues must be identified and prioritized.

Priority knowledge gaps

The top three most influential areas for the health impact of decaBDE were identified.

Environmental transformation was one of them. This was in agreement with a recent review (Vonderheide et al. 2008). The high abundance and temporal build-up measured in some environmental media are a cause for concern because of the evidences of transformational processes (Ross et al. 2008). If bromine is cleaved off from the decaBDE molecule in nature, the compound is transformed into other compounds, e.g. the lower brominated congeners which are already banned due to their accumulating properties and toxic nature (Ross et al. 2008).

Ingestional exposure was another important area that should be prioritized. There is too little knowledge on the extent of oral exposure in humans, from food and dust. There are data suggesting high exposure in children (Costa and Giordano 2007)

Toxicokinetics was a third very important area with high influence on the extent of potential health risks posed by decaBDE. Toxicokinetics is the study of how a substance gets into the body and what happens to it in the body. The special concern in this area is to what extent decaBDE is metabolised in the body to other more accumulating and toxic substances, e.g. the less brominated BDEs instead of being readily excreted as reviewed by (U.S.Environmental Protection Agency 2008). The importance of this as a priority research area is supported by Frederiksen et al. 2008

There is certainly a need for more research in these areas and also monitoring of levels in humans should be a tool to get a better overview of the exposure situation.

Also, toxicological health effects were considered an important area to prioritize, and stopping production was mentioned as an effective action to prevent potential adverse effects.

There was disagreement amongst experts as to whether conducting more scientific research would yield decisive knowledge on the risks of decaBDE within the next five years. While most experts were either highly confident or meant that sufficient knowledge already exists, others claimed that high quality research requires more time. Most experts moreover had medium to high confidence in the possibility that policy actions to effectively manage the health risks of decaBDE will become technically (not politically) feasible within the next five years.

Weight of knowledge

Arguments for using the precautionary principle to ban or restrict the use of decaBDE would be the environmental abundance and increasing levels as described by Ross et al. 2008 combined with the uncertainties and potential threats in the "priority elements" described above and in recent reviews and reports (U.S.Environmental Protection Agency 2008; Costa and Giordano 2007). The effects observed in animal studies involve brain development and hormone balance which are regarded important for risk assessment. There is also a risk that other effects appear at lower doses as further research is done. Then the environmental load will have extensive consequences. Lessons from earlier used persistent compounds should favour precaution. Transport of the compound over long distances is indicated by the concentrations measured in remote areas far away from the site of production and use (Vonderheide et al. 2008). For some uses, alternative compounds exist (European Chemicals Bureau et al. 2007) which at least are not persistent. One expert considered restrictions and prohibitions of the compound ethically justified, stating that it is unethical to pollute a whole population in order to prevent some fires. The same expert also pointed out that studies performed on certain other persistent organic compounds (TCDD, HxCB) constitute a sufficient basis to justify, by analogy, concerns about the health effects of decaBDE to humans ((Bouwman et al. 1992; Bouwman et al. 1999; Pacyniak et al. 2007). Other experts strongly disagreed and underlined that decaBDE never has been considered dioxin-like, or that decaBDE shares common properties with TCDD and HxCB, that could justify analogy.

There were also other arguments against a ban. The industry may take into use compounds which are less studied and not been subjected to risk assessment (European Chemicals Bureau et al. 2007). Also, the existing knowledge does not necessitate a ban, e.g. that few toxicological studies exist and that there is lack of knowledge regarding the margin of exposure; maybe the human exposure is not big enough for causing effects. The toxicological activity appears to be lower of the decaBDE itself compared to BDEs with less bromines (Costa and Giordano 2007).

Based on the answers from the questionnaire and discussion at the workshop, the invited experts were not in agreement on whether or not the knowledge currently available is sufficient to justify more strict policy actions at this point. While most experts felt that the persistence of decaBDE and the transformation into bioaccumulating and toxic compounds are enough to justify a ban or restrictions on use, others felt that more data is required before a decision to change the status quo is justified.

RECOMMENDATIONS

- There is a need for more research and monitoring on the substance to better support policy on this substance. Priority areas were defined as:

    1. Environmental transformation of decaBDE into related lower brominated compounds with known abilities to accumulate in the body and known toxic effects
    2. To what extent humans are exposed to decaBDE, in particular *in utero,* through food, mother's milk and dust.
    3. The toxicokinetic properties of the compound, with special focus on the potential breakdown of decaBDE to the lower brominated BDEs in the human body.

- Suggestions for improving knowledge could be:

    1. To require more research and toxicological testing from the industry itself.
    2. Better organised research cooperation between universities at the European level
    3. Better funding for relevant research.

- There is a need for information on alternative substances.

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ANNEX 1: ALL QUESTIONNAIRES

TOPIC 1: ASTHMA AND ALLERGIES

CLIMATE CHANGE: PART A - EVALUATION OF THE STRUCTURE AND COMPLETENESS OF THE CAUSAL DIAGRAM

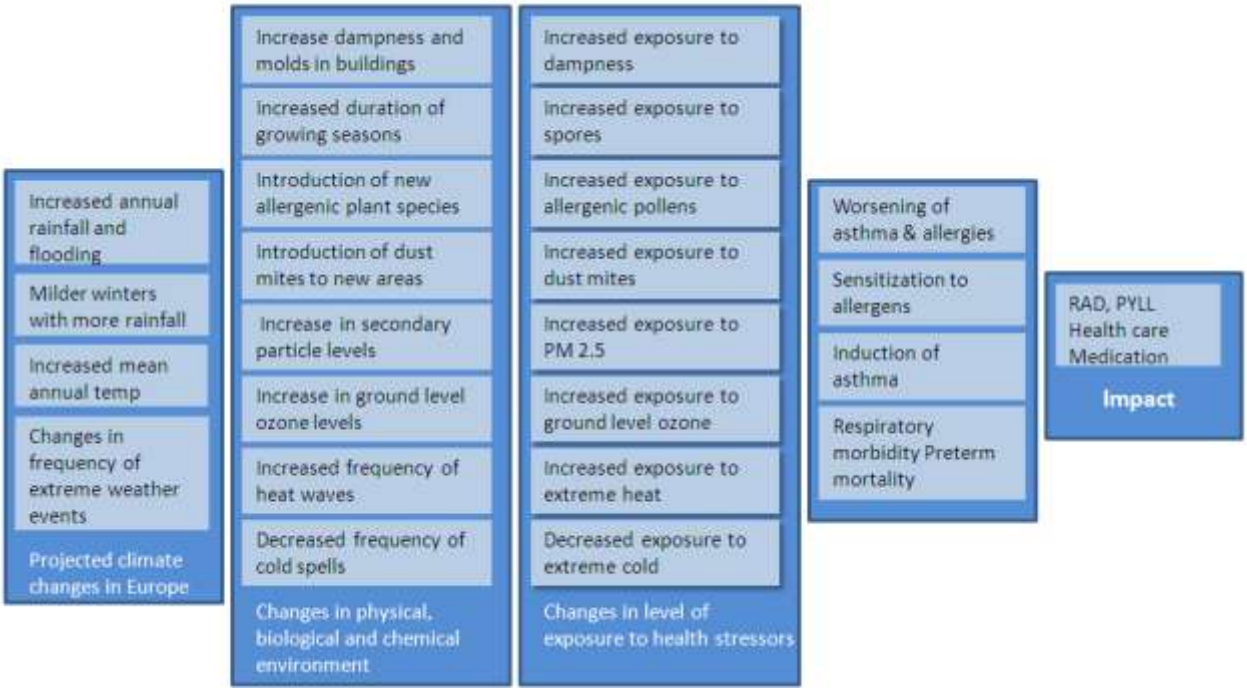


Figure 1. The diagram illustrates 8 different causal pathways through which climate change could lead to a change in cardio-respiratory mortality and morbidity rates:

Changed exposure to PM2.5

Changed exposure to ground level ozone

Changed exposure to dust mites

Changed exposure to allergenic pollens

Changed exposure to extreme heat

Decreased exposure to extreme cold

Changed exposure to mould spores

Changed exposure to damp buildings and wet building materials.

Evaluate the completeness of the diagram by answering the following questions.

1. Does the diagram take into account all of the important parameters when evaluating the asthma and allergy risks related to climate change? If no, please explain.

_____
_____
_____
_____

2. Are the different causal relationships adequately structured? If no, please explain.

_____
_____
_____
_____

3. Are there any unnecessary parameters shown in the diagram that could be deleted? If yes, please explain.

_____
_____
_____
_____

PART B - EVALUATION OF INDIVIDUAL CAUSAL ELEMENTS

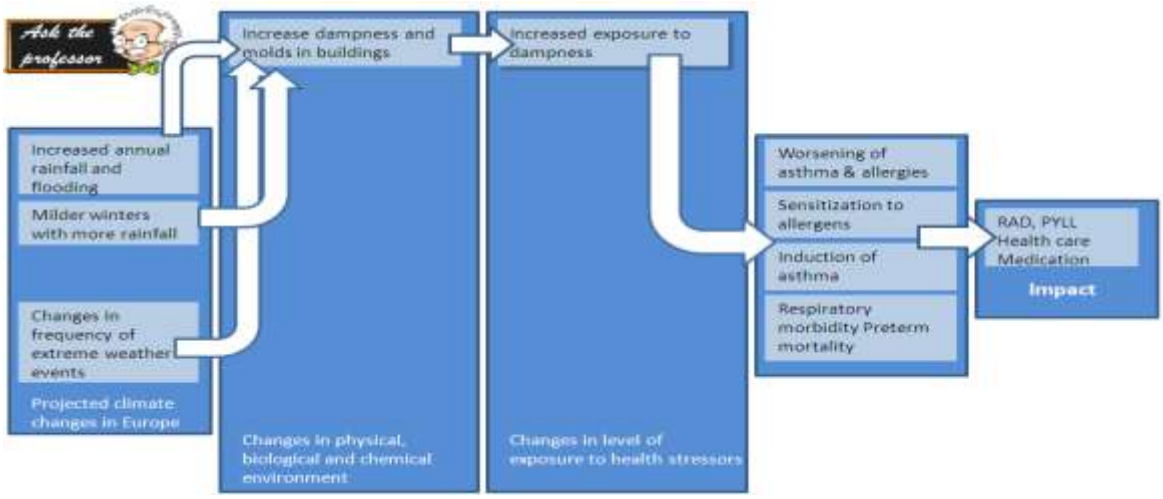
In the following section, we ask you to express your level of confidence in the claims that specific effects are expected to occur as a result of a change in the factor(s) representing the previous model module.

Please consider each question independently of the others. For example, when you answer a question on confidence in health effects, do not let your answer be influenced by your answer on your confidence in changes in exposure levels.

The level of confidence scheme used in the questionnaire follows the guidelines below.

Very high confidence. At least a 9 out of 10 chance of being correct.	High confidence. At least an 8 out of 10 chance of being correct.	Medium confidence. At least a 5 out of 10 chance of being correct.	Low confidence. At least a 2 out of 10 chance of being correct.	Very low confidence. Less than a 1 out of 10 chance of being correct.

1.Changed exposure to dampness



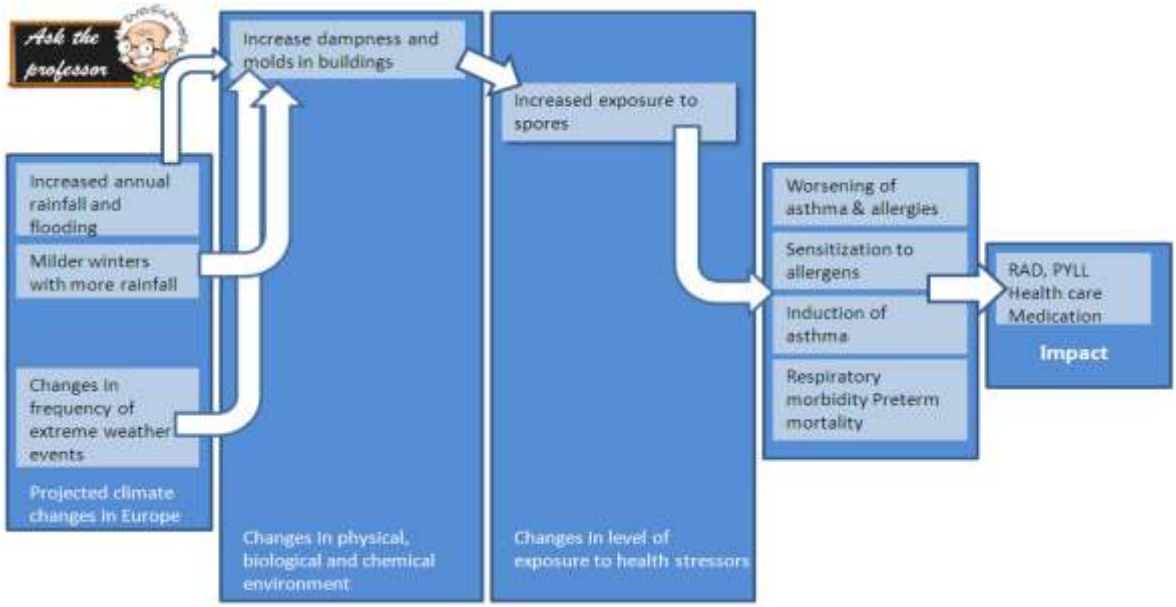
1.1 What is your level of confidence in the claim that increased rainfall and flooding from climate change will increase the numbers of damp buildings and wet building material?

1.2 What is your level of confidence in the claim that population exposure to damp buildings and wet building material also will increase as a result of climate change?

1.3 What is your level of confidence in the claim that increased exposure to damp buildings and wet building material will increase the frequency of acute asthma and respiratory morbidity?

1.4 What is your level of confidence in the claim that increased exposure to damp buildings and wet building material will result in an increased incidence/prevalence of asthma and/or allergies?

2. Changed exposure to moulds and spores



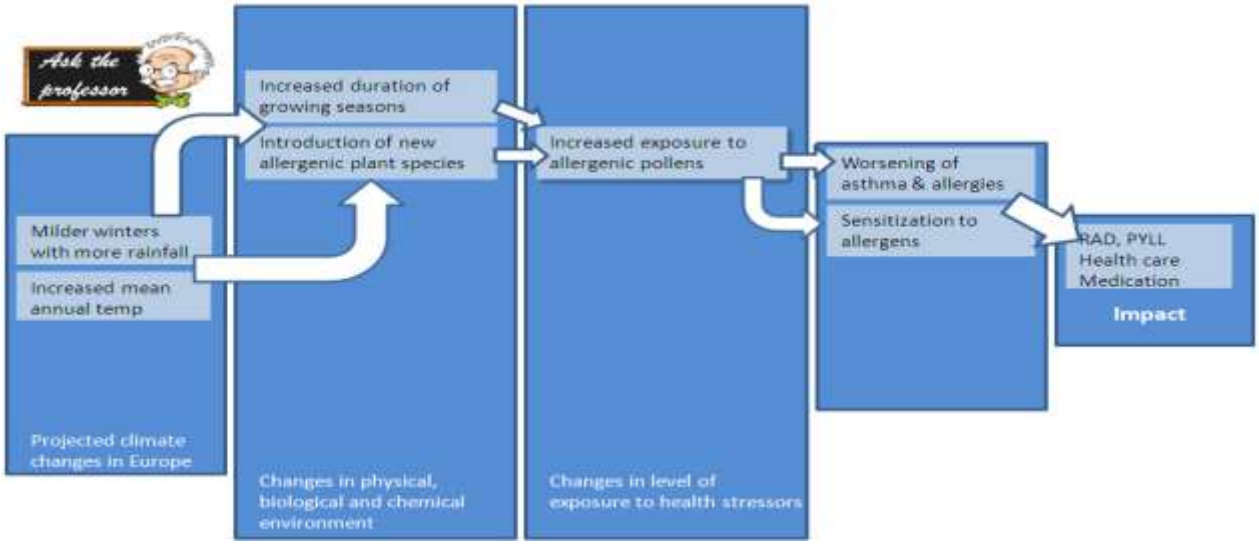
2.1 What is your level of confidence in the claim that increased rainfall and flooding from climate change will result in increases in moulds and spores in buildings?

2.2 What is your level of confidence in the claim that the exposure of the population to moulds and spores in the buildings also will increase as a result of climate change?

2.3 What is your level of confidence in the claim that increased exposure to moulds and spores in buildings will increase the frequency of acute asthma and respiratory morbidity?

2.4 What is your level of confidence in the claim that increased exposure to moulds and spores will result in an increased incidence/prevalence of asthma and/or allergies?

3.Changed exposure to allergenic pollen



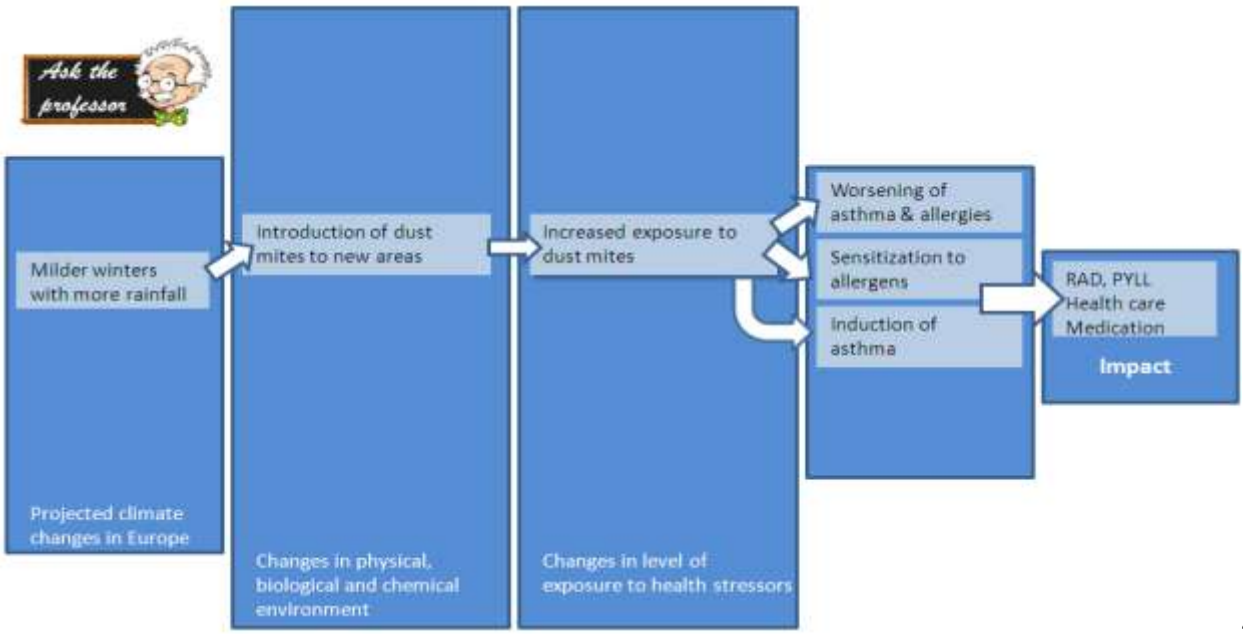
3.1 What is your level of confidence in the claim that climate change will result in increased levels of allergenic pollen?

3.2 What is your level of confidence in the claim that increased levels of allergenic pollen from climate change also will result in an increased population exposure?

3.3 What is your level of confidence in the claim that increased exposure to allergenic pollen will increase the frequency of acute asthma and respiratory morbidity?

3.4 What is your level of confidence in the claim that increased exposure to allergenic pollen will result in an increased incidence/prevalence of asthma and/or allergies?

4. Changed exposure to dust mites



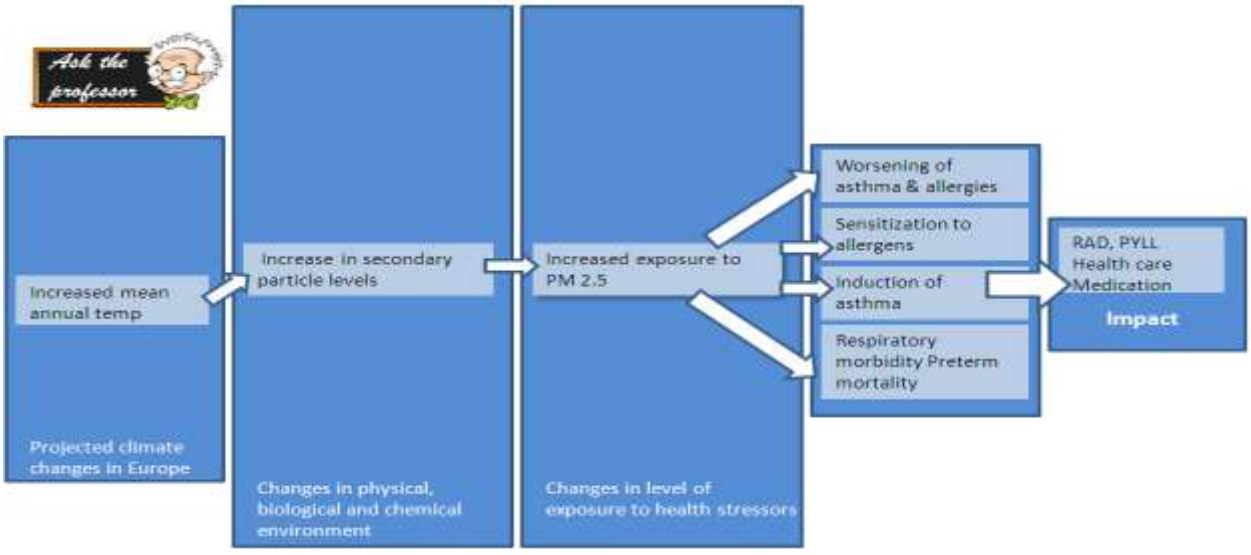
4.1 What is your level of confidence in the claim that climate change will result in increased levels of dust mites?

4.2 What is your level of confidence in the claim that increased levels of dust mites from climate change also will result in an increased population exposure?

4.3 What is your level of confidence in the claim that increased exposure to dust mites will increase the frequency of acute asthma and respiratory morbidity?

4.4 What is your level of confidence in the claim that increased exposure to dust mites will result in an increased incidence/prevalence of asthma and/or allergies?

5. Changed exposure to PM2.5



5.1 What is your level of confidence in the claim that climate change will result in increased levels of secondary fine (PM2.5) particles?

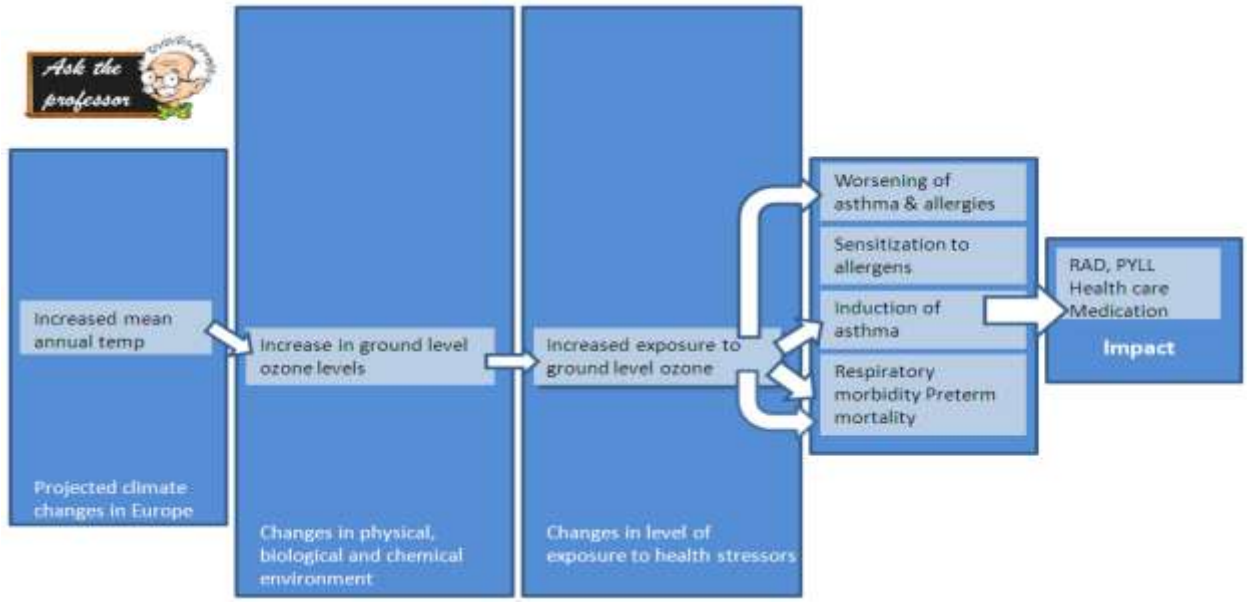
5.2 What is your level of confidence in the claim that increased levels of secondary fine (PM2.5) particles also will result in an increased population exposure?

5.3 What is your level of confidence in the claim that increased exposure to secondary fine (PM2.5) particles will increase the frequency of acute asthma and respiratory morbidity?

5.4 What is your level of confidence in the claim that increased exposure to secondary fine (PM2.5) particles will result in an increased incidence/prevalence of asthma and/or allergies?

5.5 What is your level of confidence in the claim that increased exposure to secondary fine (PM2.5) particles will result in an increase in cardiorespiratory mortality rates?

6. Changed exposure to ozone



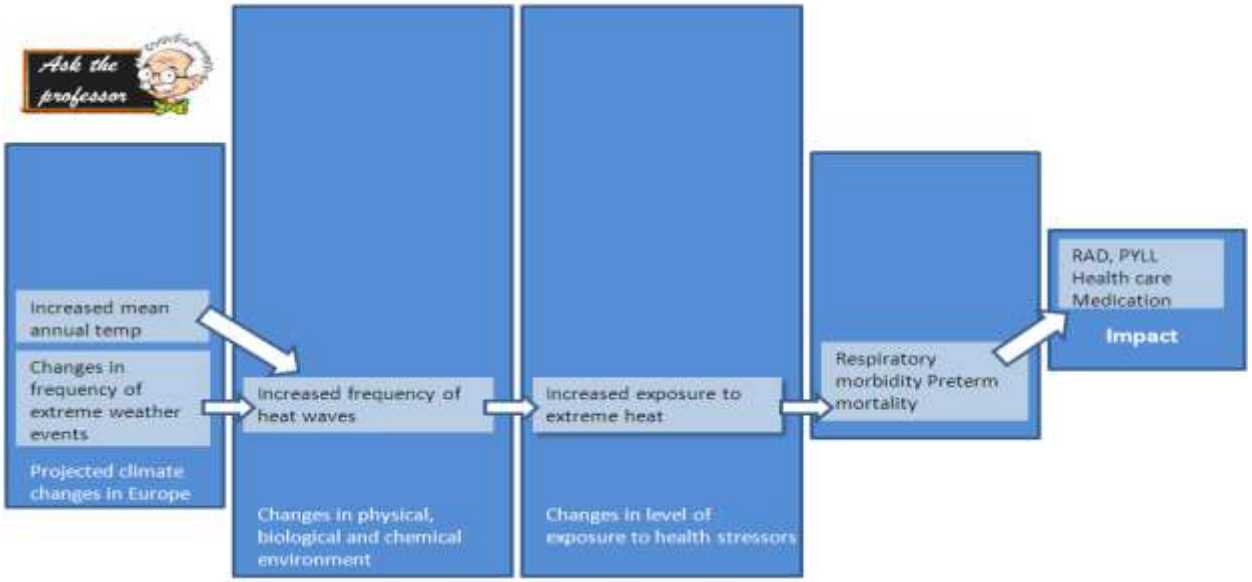
6.1 What is your level of confidence in the claim that climate change will result in increased concentrations of ground level ozone?

6.2 What is your level of confidence in the claim that increased ground levels of ozone also will result in an increased population exposure?

6.3 What is your level of confidence in the claim that exposure to increased ground levels of ozone will increase the frequency of acute asthma and respiratory morbidity?

6.4 What is your level of confidence in the claim that exposure to increased ground levels of ozone will result in an increased incidence/prevalence of asthma and/or allergies?

7. Changed exposure to extreme heat

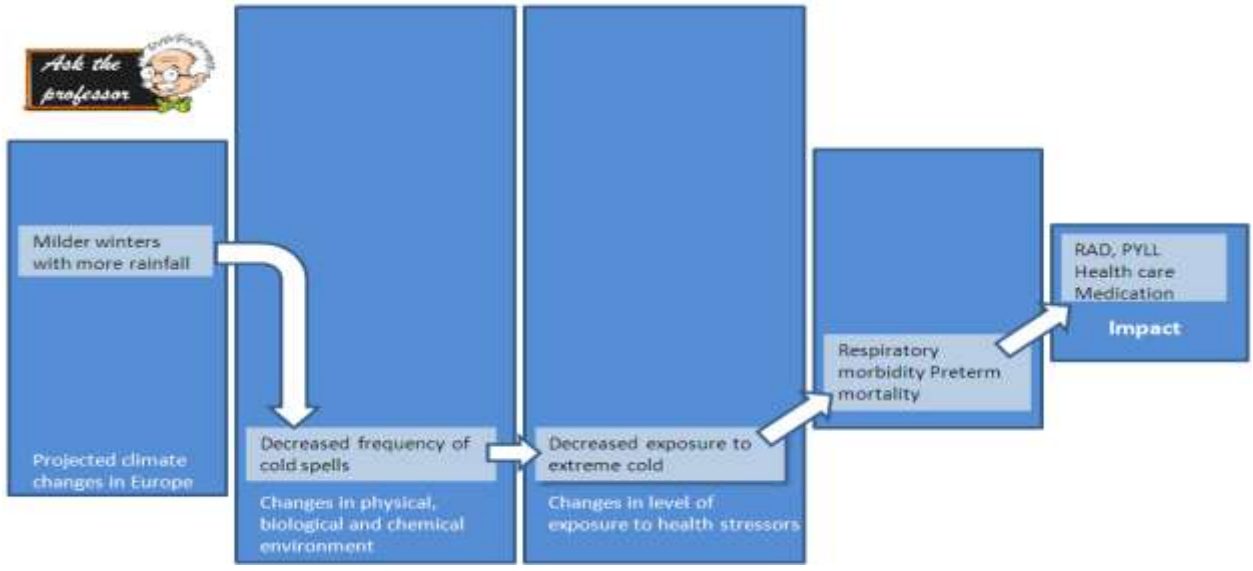


7.1 What is your level of confidence in the claim that climate change will result in increased frequency and duration of heat waves?

7.2 What is your level of confidence in the claim that population exposure to extreme heat also will increase as a result of climate change?

7.3 What is your level of confidence in the claim that cardio respiratory mortality and/or morbidity will increase as a result of increased exposures to extreme heat?

8. Decreased exposure to extreme cold



8.1 What is your level of confidence in the claim that climate change will result in decreased frequency and duration of cold spells?

8.2 What is your level of confidence in the claim that population exposure to extreme cold also will decrease as a result of climate change?

8.3 What is your level of confidence in the claim that cardio respiratory mortality and/or morbidity will decrease as a result of decreased exposures to extreme cold?

9. Cross cutting issues

9.1 The diagram in figure 1 illustrates 8 different causal pathways through which climate change could lead to a change in cardio-respiratory mortality and morbidity rates. These pathways are listed below. On a scale of 1 to 8, please rank the relative importance of each pathway, in comparison with the health impact to be expected via other pathways.

Causal Pathway	Relative ranking (1-8)
Changed exposure to PM2.5	_____
Changed exposure to ground level ozone	_____
Changed exposure to dust mites	_____
Changed exposure to allergenic pollens	_____
Changed exposure to extreme heat	_____
Decreased exposure to extreme cold	_____
Changed exposure to mould spores	_____
Changed exposure to damp buildings and wet building material	_____

10. The 8 causal pathways shown in the diagram will interact with one another and lead to a combined impact on health. While the combined health impacts of some of the 8 causal pathways may be additive, others could possibly interact in a synergistic or antagonistic way.

With this in mind, what is your level of confidence in our ability to predict the magnitude of the overall impact of climate change on respiratory morbidity and mortality rates?

Final comments

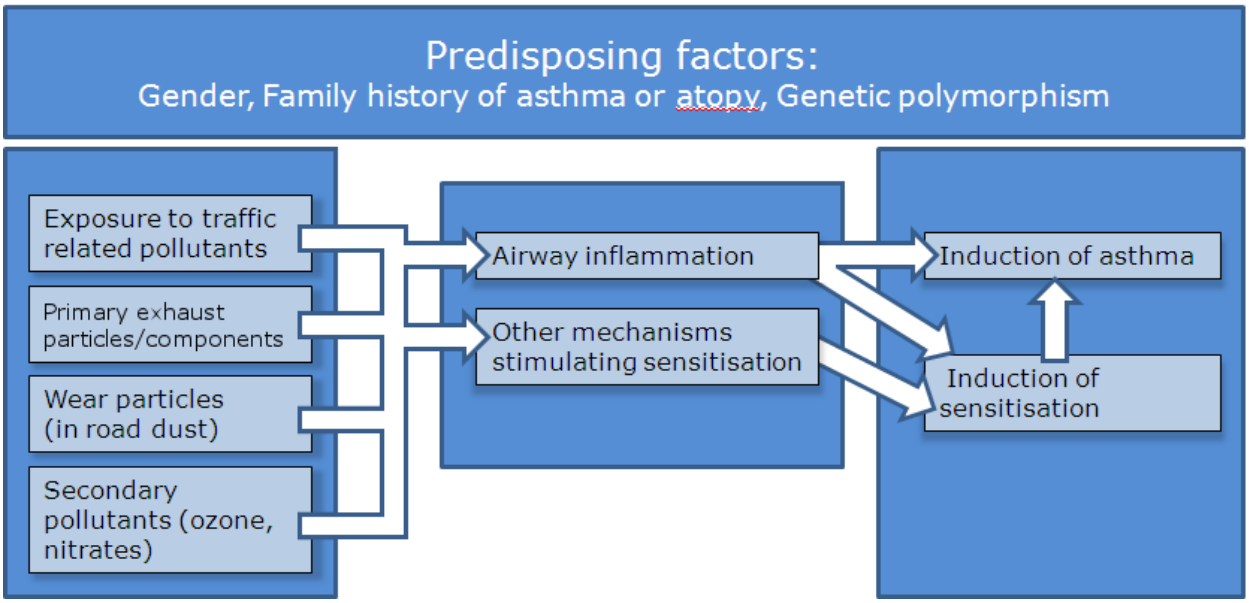
Are there any comments you would like to make in closing to complete your evaluation? Perhaps you would like to comment on key areas of knowledge which you think are underdeveloped?

Perhaps you would like to provide your impressions of the usefulness of this evaluation, or provide suggestions on how to improve it?

_____

_____

_____



1. Does the diagram take into account all of the important parameters when evaluating the asthma and allergy risks related to traffic pollutants? **YES/NO**

If No, please explain:

2. Are the different causal relationships adequately structured? . **YES/NO**

If No, please explain:

3. Are there any unnecessary parameters shown in the diagram that could be deleted?

YES/NO

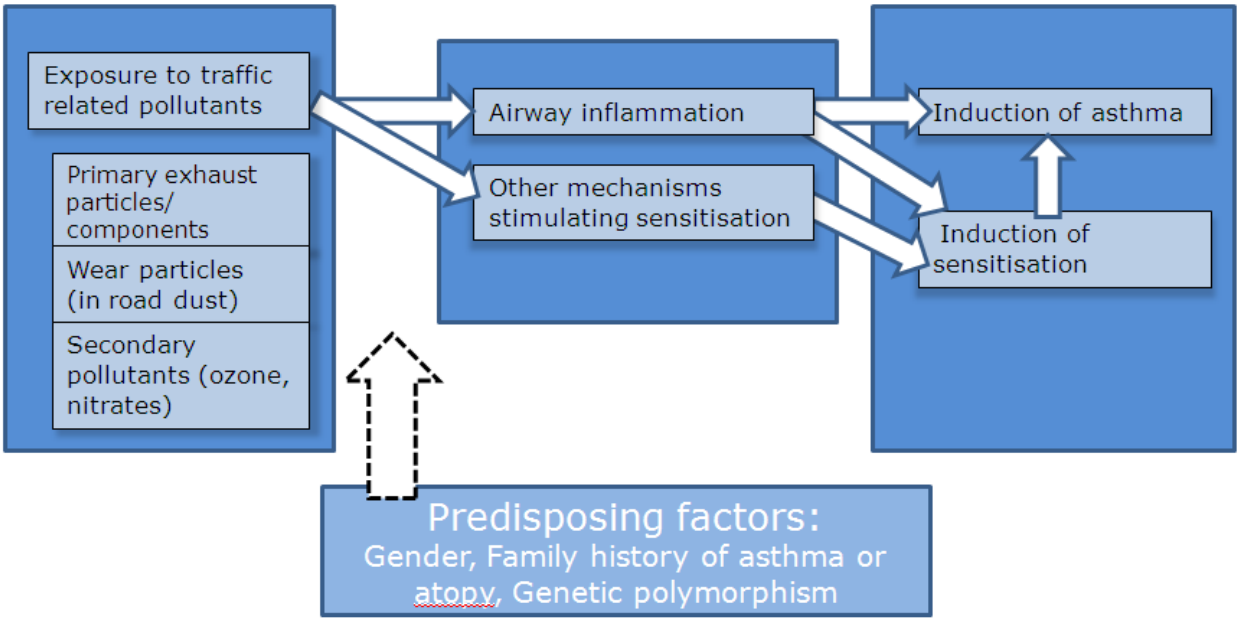
If Yes, please explain:

PART B - EVALUATION OF INDIVIDUAL CAUSAL ELEMENTS

When questions ask for your level of confidence, please use the guidelines below:

4. Very high confidence.	3. High confidence.	2. Medium confidence.	1. Low confidence.	0. Very low confidence.
At least a 9 out of 10 chance of being correct.	At least an 8 out of 10 chance of being correct.	At least a 5 out of 10 chance of being correct.	At least a 2 out of 10 chance of being correct.	Less than a 1 out of 10 chance of being correct.

1. Associations related to road traffic pollution



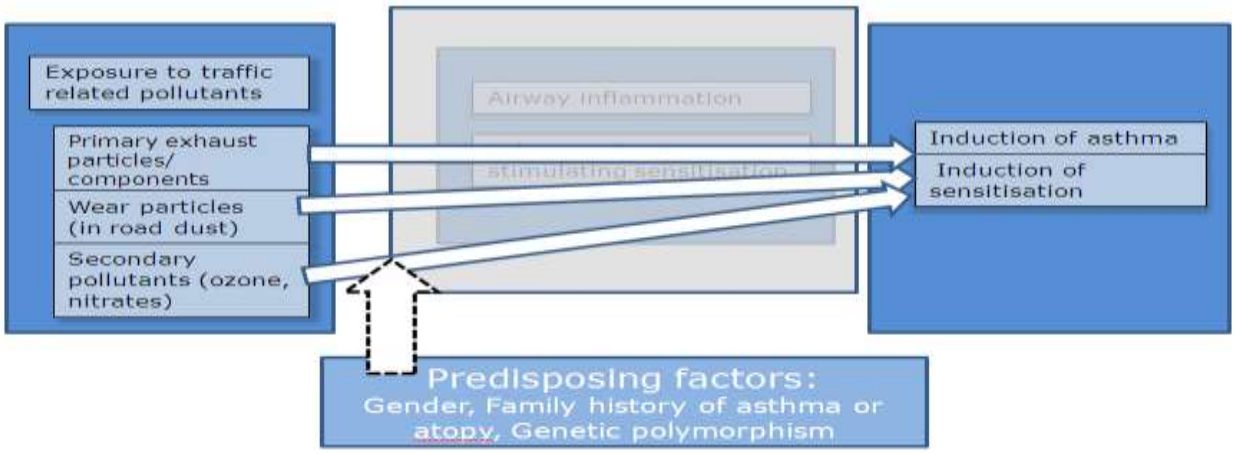
1. What is your level of confidence in our ability to predict the magnitude of the effect of road traffic related air pollutants on inflammation in the lungs?

2. What is your level of confidence in our ability to predict the magnitude of the effect on asthma induction related to inflammation in the lungs?

3. What is your level of confidence in our ability to predict the magnitude of the effect on induction of sensitisation related to inflammation in the lungs?

4. What is your level of confidence in our ability to predict the magnitude of other mechanisms (than inflammation) by which road traffic related air pollutants has an effect on induction of sensitisation?

2. Associations related to selected pollutant related to road traffic



5. What is your level of confidence in our ability to predict the magnitude of the effect of *primary exhaust particles/components* on induction of asthma and sensitisation (by any mechanism)?

6. What is your level of confidence in our ability to predict the magnitude of the effect of *wear particles* (in road dust) on induction of asthma and sensitisation (by any mechanism)?

7. What is your level of confidence in our ability to predict the magnitude of the effect of *traffic related secondary pollutants (nitrates, ozone etcetera)* on induction of asthma and sensitisation (by any mechanism)?

3. Cross cutting issues

The diagram illustrates different proposed or potential ways through which traffic exposure could lead to induction of asthma and/or sensitisation. On a scale of 1 to 6, please rank the relative importance of each proposed or potential association in comparison with the health impact to be expected via other pathways.

Causal Pathway	Relative ranking (1-6)
1. Primary exhaust components – Induction of asthma	_____
2. Primary exhaust components – Induction of sensitization	_____
3. Wear particles – Induction of asthma	_____
4. Wear particles – Induction of sensitization	_____
5. Secondary pollutants – Induction of asthma	_____
6. Secondary pollutants – Induction of sensitisation	_____

4. Final comments

Are there any comments you would like to make in closing to complete your evaluation? Perhaps you would like to comment on key areas of knowledge which you think are underdeveloped?

Answer:

TOPIC 2: CANCER

Current state of the art

Before evaluating the diagrams, please take your take you time to read the general considerations summarised on the next page, which gives an overview of the environment-cancer issue and - most important - the methodology that has been followed in constructing the diagrams (the best scientific evidence available and the strength of association).

Cancer accounted for more than 7 million deaths worldwide in 2000, and 10 million new cancer cases were diagnosed. More than 60% of cancer deaths occurred in the developing regions. Lung cancer was the most common, followed by cancers of the stomach, liver, colon and rectum, and breast. Cancer in all ages is a result of the interaction between age, genetic and environmental factors. Differences in lifestyle and environmental exposures have been assumed to be a major reason for the various geographical distribution of cancer. Genetic factors and ethnic variations account for some part of regional differences (EEA report 10/2005).

Environmental factors are important in the pathogenesis of cancer, but if lifestyle-related environmental factors are excluded, the only environmental factor for which there is a proven connection to cancer development is ionising radiation. The carcinogenic effect of it arises through direct damage to DNA. The connection between non-ionising radiation and skin cancer is also well established: Approximately 80-90% of all skin cancers can be related to UV radiation.

There is a scientific debate that long-term, low-dose exposure to both low and high frequency electromagnetic fields can cause adverse health effects. Indeed recent systematic reviews showed a statistical association between low and high frequency electromagnetic fields and childhood leukaemia and brain tumors. However, the mechanisms by which these weak fields could cause leukaemia or brain tumors remain unclear and the evidence is not conclusive.

Some chemicals clearly cause cancers in some exposed groups, but the role of chemicals in overall cancer causation is unclear and disputed. Any excess cancer mortality from a chemical pollutant is likely to be restricted to a section of the population, so mortality rates for entire populations can often be weak and insensitive indicators of environmental health effects from pollution. Moreover, people are exposed indoor and outdoor to complex mixtures present in air, water, and food. Air pollution, for example, includes carcinogenic chemicals such as benzene and polycyclic aromatic hydrocarbons (PAH). Fried and smoked food items may contain carcinogenic substances as well.

Several studies showed a positive association between local traffic density and childhood leukaemia. Only a limited number of studies have evaluated the potential risk of living nearby hazardous industrial sites, which may also be a source of carcinogenic chemicals.

Cancer in European children younger than 15 years is in general terms rare, but is still one of the most common causes of death in children in industrialised countries. The most common childhood cancers are leukaemia and brain tumours. A small but significant increase in childhood cancers has been noted since the mid- 1980s, which could have been explained by better diagnostic methods, but an additional component from environmental exposures cannot be excluded.

Children are particularly at risk from chemicals because of their greater biological sensitivity and greater exposure to environmental pollution relative to body weight. Although no specific parental occupational exposure was definitely established as a cause of childhood cancer, several occupations have been found to be statistically associated with it: increased risk of brain cancer has been related to maternal exposure to

high levels of solvents; occurrence of brain tumours has been related to paternal exposure to pesticides and PAH.

Many studies suggest that most cancers in children are initiated before birth. Greater susceptibility of the foetus and young child has physiological reasons since they are undergoing multiple processes of growth and differentiation and the potential for mutations to arise following transplacental exposure to a carcinogen is therefore much greater in the growing foetus and child. Chemical pollutants which are carcinogens and that may affect reproductive health and newborn children include certain metals (e.g. lead and methyl mercury), pesticides (e.g. DDT), and industrial chemicals (e.g. PCBs). .
Exposure to exogenous carcinogens in childhood may have an important effect on cancer risk in adult life. Recent epidemiological studies have demonstrated the important role of genetic susceptibility in cancer development. Individual susceptibility to cancer may result from several host factors including differences in metabolism, DNA repair, altered expression of protooncogenes and tumour suppressor genes. Since most carcinogens require metabolic activation before binding to DNA, individual features of carcinogen metabolism may facilitate or help to block the development of environmental cancer.

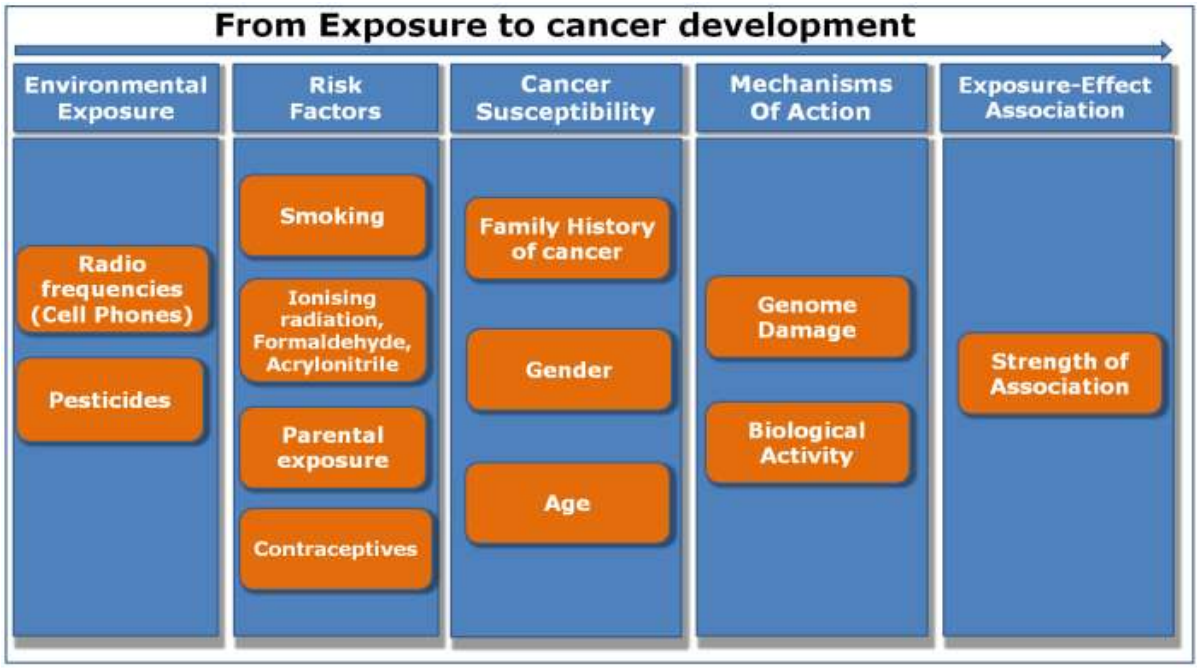
Figure 4: Hierachy of different research designs, ranked from weakest to strongest.

The evidence of the exposure-effect association (causal association) in human studies comes from different study designs. Some designs are considered to provide a stronger level of evidence than others. Based on their inherent characteristics their hierarchy is graphically summarized in a pyramid. The pyramid depicts the strength of the evidence for commonly used research designs (from the weakest to the strongest). Such hierarchy should be taken into account in evaluating the published evidence.

When questions ask for your level of confidence, please use the guidelines below:

Very high confidence.	High confidence.	Medium confidence.	Low confidence.	Very low confidence.
At least 9 in 10 chance of being correct	At least 7 in 10 chance of being correct.	At least 5 in 10 chance of being correct.	At least 3 in 10 chance of being correct.	Less than 2 out of 10 chance of being correct.

BRAIN CANCER

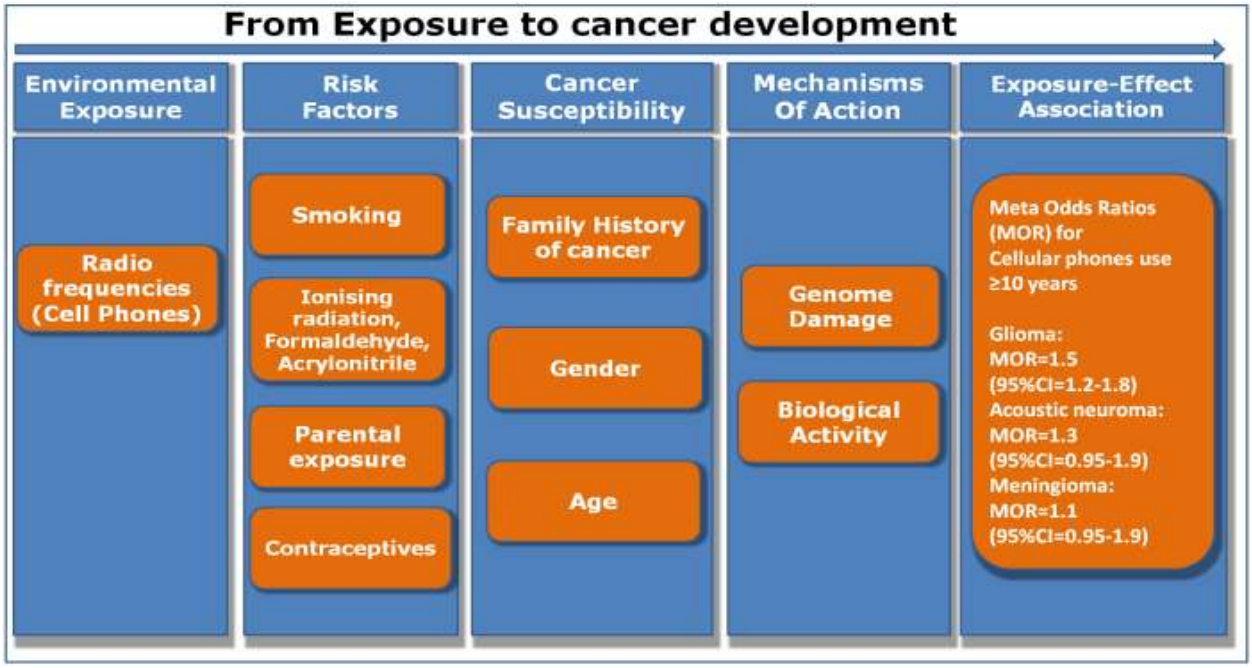


There are more than 120 types of brain tumors. Today, most medical institutions use the World Health Organization (WHO) classification system to identify brain tumors (WHO Classification of Tumors of the CNS, 2007). The WHO classifies brain tumors by cell origin and how the cells behave.

Tumors of neuroepithelial tissue (astrocytic tumors) (oligodendroglial tumors) (oligoastrocytic tumors) (ependymal tumors) (choroid plexus tumors) (other neuroepithelial tumors) (neuronal and mixed neuronal – glial tumors) (tumors of the pineal region) (embryonal tumors)*Tumors of cranial and paraspinal nerves* (other neoplasms related to the meninges)	Tumors of the meninges (tumors of meningothelial cells) (mesenchymal tumors) (primary melanocytic lesions) *Lymphomas and hematopoietic neoplasms* *Germ cell tumors* *Tumors of the sellar region* *Metastatic tumor*

It is important important to note benign brain tumors located in a vital area can be considered life–threatening and just as difficult to treat as malignant brain tumors.

BRAIN TUMORS – RADIOFREQUENCIES



RISK FACTORS

SMOKING

Cigarette smoke contains formaldehyde a chemical know to cause brain tumors.

IONISING RADIATION, FORMALDEHYDE, ACRYLONITRILE.

Increased risk of brain tumor has been reported in occupationally exposed workers.

PARENTAL EXPOSURE

Parental exposure to solvents has been associated with brain tumors in children.

CONTRACEPTIVES

Increased risk in women who used long-acting hormonal contraceptives (>= 10 years): OR= 2.7 (95%CI, 0.9-7.5).

CANCER SUSCEPTIBILITY

FAMILY HISTORY OF CANCER

There is evidence that subjects with family members who have gliomas (a specific type of brain cancer) may have a high risk to develop glioma.

GENDER

Brain tumors occur more frequently in males than in females.
Meningiomas are more common in females than in males.

AGE

Radiofrequencies exposure (SAR, i.e., specific absorption rate) of peripheral brain sub-regions are two times higher in children than in adults: skin and bone layers in children are thinner in children.
Brain tumors are the second most common cancer in children and are more common in children aged <8 years.

MECHANISMS OF ACTION

GENOME DAMAGE
Radiofrequency radiation may enhance chemically induced reactive oxygen species production and DNA damage. Radiofrequency in vitro causes increased levels of aneuploidy.

BIOLOGICAL ACTIVITY
Radiofrequency causes production of free radicals

Questions

What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to radiofrequency from using cell phones and the risk of brain tumours?

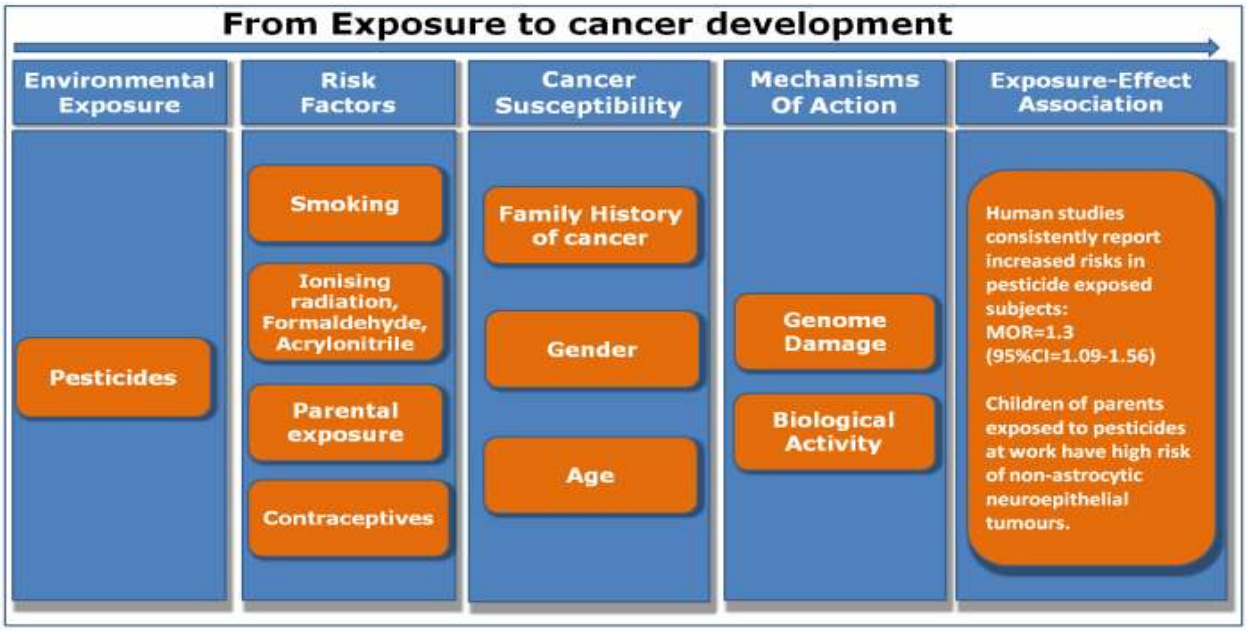
What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to radiofrequency and cancer risk?

Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle)?

In favor ☐ Against ☐

If you have any specific policy actions in mind, please specify them here:

BRAIN CANCER – PESTICIDES



RISK FACTORS

SMOKING

Cigarette smoke contains formaldehyde a chemical know to cause brain tumors.

IONISING RADIATION, FORMALDEHYDE, ACRYLONITRILE

Increased risk of brain tumor have been reported in occupationally exposed subjects.

CONTRACEPTIVES

Increased risk in women who used long-acting hormonal contraceptives (>= 10 years): OR= 2.7 (95%CI, 0.9-7.5).

PARENTAL EXPOSURE

Parental exposure to solvents has been associated with brain tumors in children.

CANCER SUSCEPTIBILITY

GENDER

Brain tumors occur more frequently in males than in females.

Meningiomas are more common in females than in males.

FAMILY HISTORY

There is evidence that subject with family members who have gliomas (a specific type of brain cancer) may have a high risk to develop glioma.

AGE

Children may be sensitive to the carcinogenic exposure to pesticides: increased risks in children are greater than in adults.

Brain tumors are the second most common cancer in children and are more common in children aged <8 years.

MECHANISMS OF ACTION

GENOME DAMAGE

Chromosome aberrations and increased frequency of micronuclei have been detected in the majority of studies, mitotic arrest, clastogens, aneugens, some pesticides cause disturbances of mitotic spindle.

BIOLOGICAL ACTIVITY

Translocations or clonotypic gene fusion sequences match that of later leukemic blasts in blood spots (Guthrie card), some pesticides are xenoestrogens, ROS production.

Questions

What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to pesticides and the risk of brain tumours?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to radiofrequency and brain cancer risk?

Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle) to reduce pesticide exposure?

In favor ☐ Against ☐

If you have any specific policy actions in mind, please specify them here:

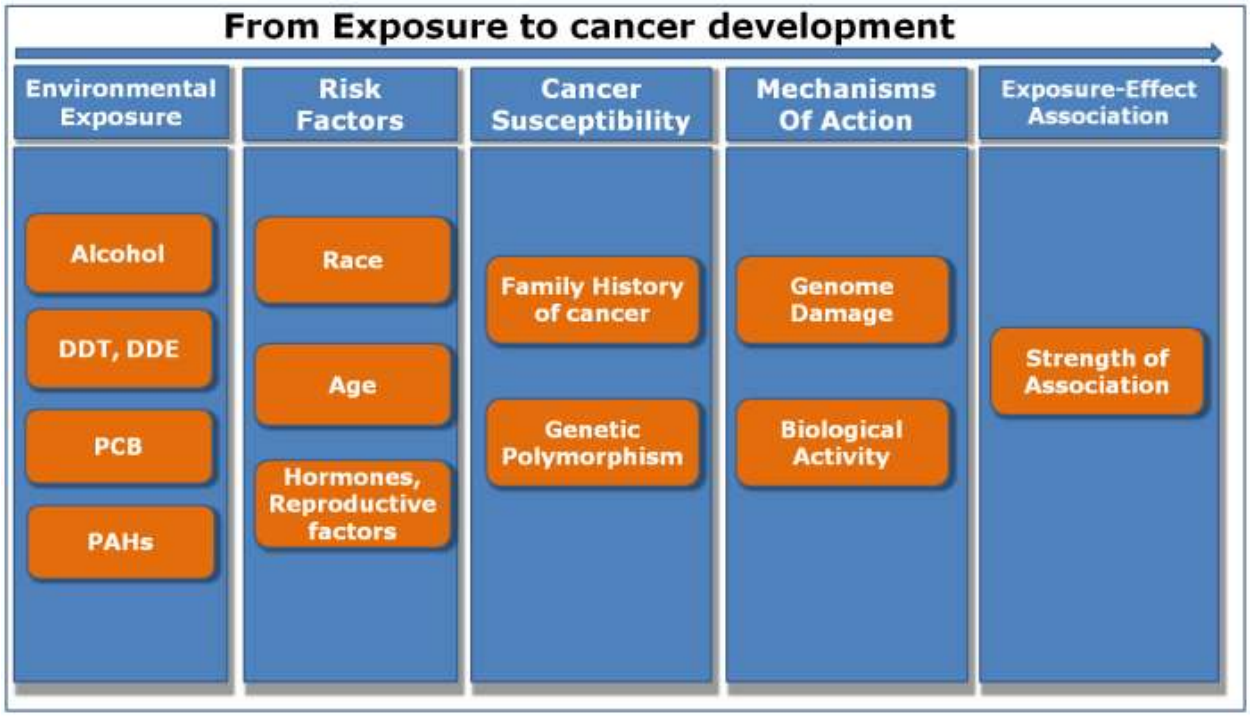
BREAST TUMORS

Benign epithelial lesions with no significant tendency to malignant transformation include:

- Adenoma:
    - Ductal
    - Lactating
    - Tubular
- Adenosis:
    - apocrine
    - Blunt duct
    - Microglandular
    - Sclerosing
- Fibroadenoma
- Radial scar/complex sclerosing lesions

Invasive breast carcinomas are divided into two major categories on the basis of their cytoarchitectural features:

- ***Invasive ductal carcinoma:***
    - Acinic cell carcinoma
    - Adenoid cystic carcinoma
    - Apocrine carcinoma
    - Cribriform carcinoma
    - Glycogen-rich/clear cell
    - inflammatory carcinoma
    - lipid-rich carcinoma
    - medullary carcinoma
    - metaplastic carcinoma
    - micropapillary carcinoma
    - mucinous carcinoma
    - neuroendocrine carcinoma
    - oncocytic carcinoma
    - papillary carcinoma
    - sebaceous carcinoma
    - tubular carcinoma
- ***Invasive lobular carcinoma:***
    - pleomorphic
    - signet ring cell



RISK FACTORS (are valid for ALL exposures).

RACE

Breast cancer risk is higher in white women than African American, Latina or Asian women.

AGE

Breast cancer risk increase with age and most cases of breast cancer occur in women over 60.
Increased risk in premenopausal women lacking for the GSTM1 and GSTT1 genes.

HORMONES

Estrogens and other hormones, including pharmaceutical hormones, and lack of exercise could affect hormone levels and reproductive characteristics, which are associated with breast cancer development.

CANCER SUSCEPTIBILITY (are valid for ALL exposures)

FAMILY HISTORY OF CANCER

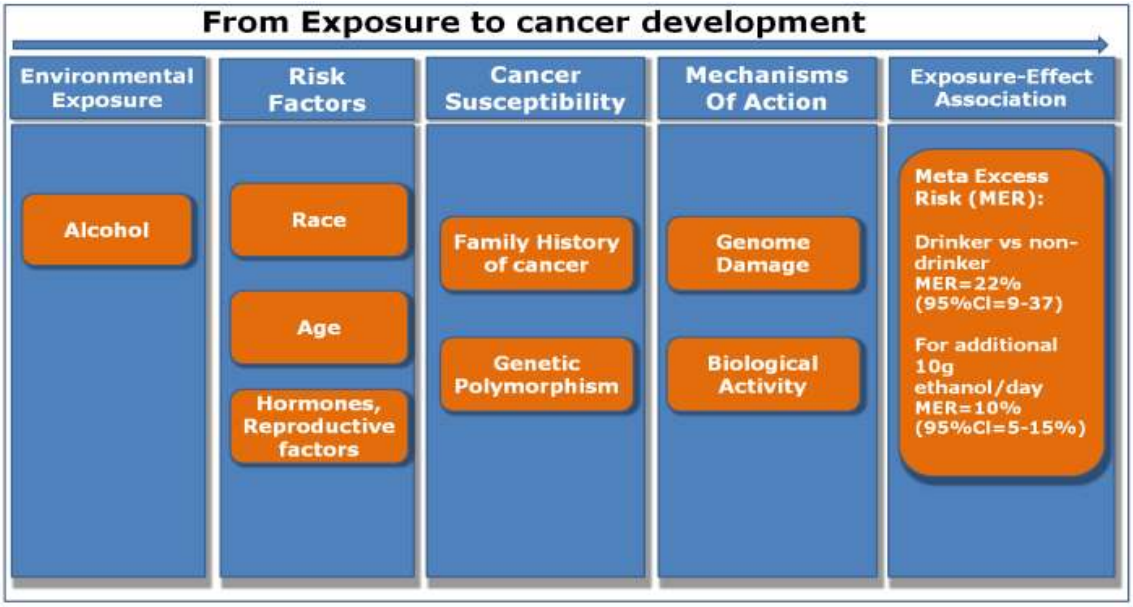
Breast cancer risk is higher if a woman first degree relative (mother, sister, daughter) had breast cancer and if a member of her family got breast cancer before age 40.
BRCA1-mutation carriers by age 70 years have a cumulative risks MCR=65% (95%CI=44%-78%) ; BRCA2-mutation carriers by age 70 years: MCR=45% (95%CI=31%-56%).

GENETIC POLYMORPHYSMS

Effect of XRCC1 polymorphisms Arg280His variant in Asian population MOR=2.27 (95%CI=0.82-6.31) and Arg399Gln variant in Asian population MOR=1.59 (95%CI=1.22-2.09).

BREAST TUMORS -ALCOHOL

MECHANISMS OF ACTION



GENOME DAMAGE

Alcohol increases frequency of chromosome aberrations, sister chromatid exchange frequency, micronucleus frequency, chromosome damage in oncogenic regions.

BIOLOGICAL ACTIVITY

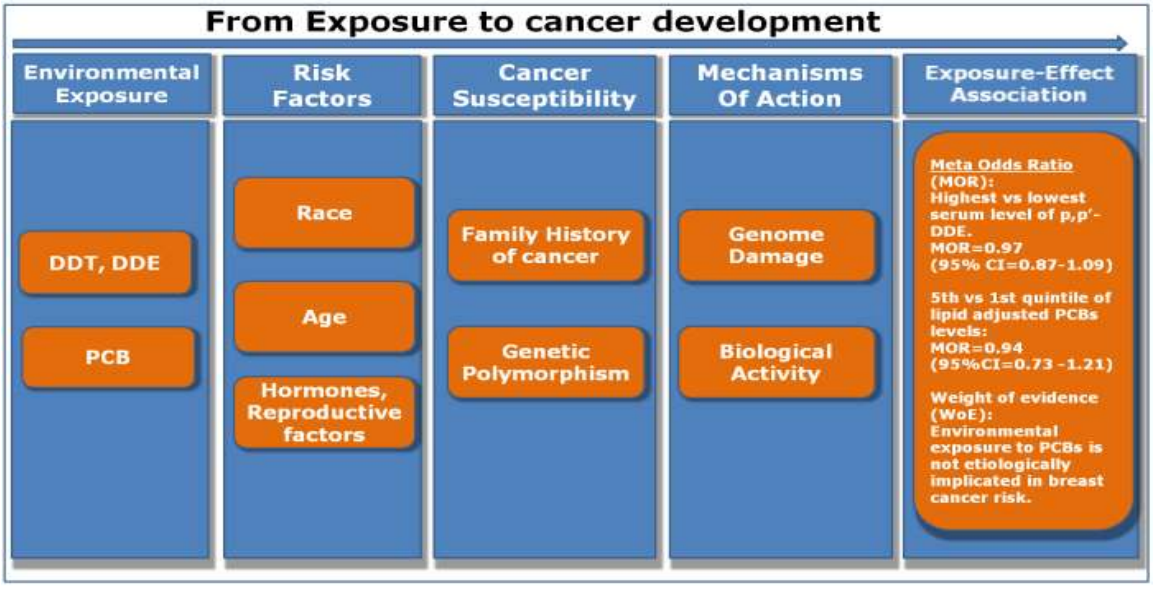
Alcohol increases estrogen levels, clastogen, aneugen, ROS production, interfers with DNA methylation.

Question

What is your level of confidence in the current scientists' ability to predict the impact of exposure to alcohol and the risk of breast cancer?

BREAST TUMORS – DDE, DDT, PCB

MECHANISMS OF ACTION



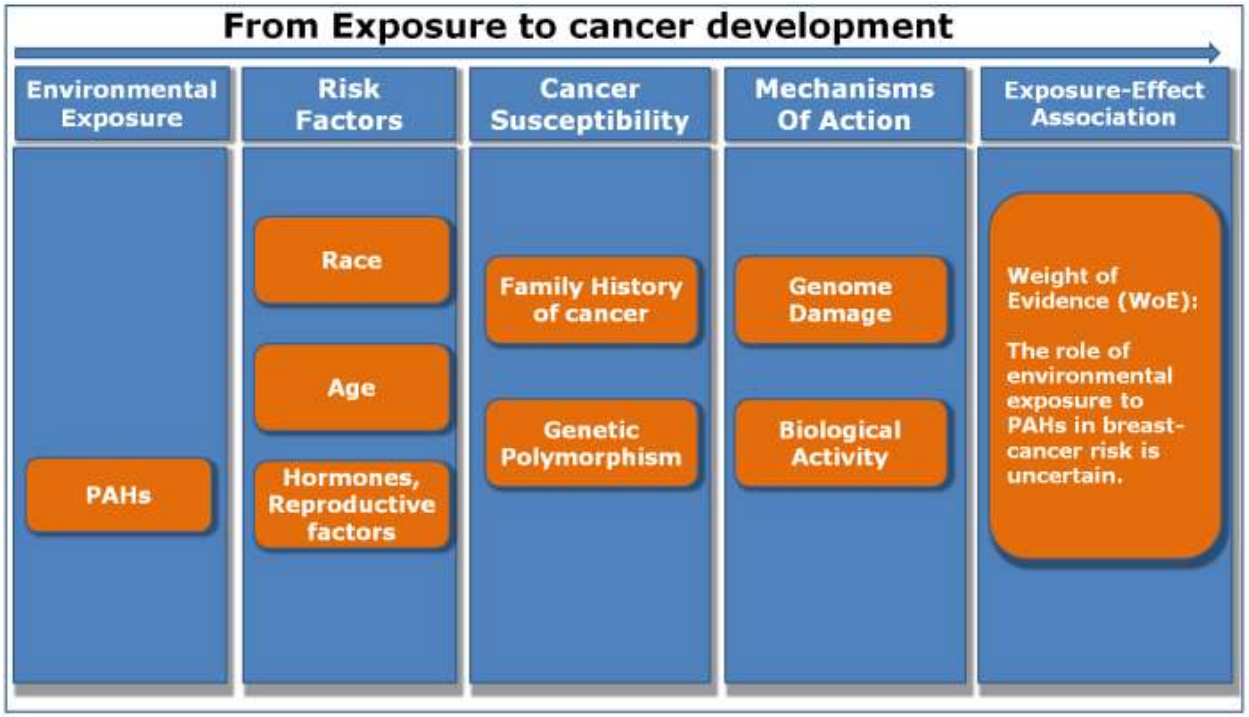
GENOME DAMAGE
Organochlorine insecticides DDT,DDE and PCB increased frequency of chromosome aberrations, sister chromatid exchange frequency, micronucleus frequency, chromosome damage in oncogenic regions.

BIOLOGICAL ACTIVITY
Organochlorine insecticides DDT,DDE and PCB increases estrogen levels, clastogen, aneugen, ROS production, interfers with DNA methylation.
Animal studies shows increased susceptibility to induced mammary tumors in rats when DDT, DDE, PCBs are given neonatally to rats.

Question

What is your level of confidence in scientists' ability to predict the effect of environmental exposure to DDT,DDE and PCB on breast cancer risk?

BREAST TUMORS -PAHS



MECHANISMS OF ACTION
GENOME DAMAGE
PAHs increase frequency of DNA adducts and chromosome damage

BIOLOGICAL ACTIVITY
Some PAHs are mammary carcinogens in laboratory animals. Poor evidence that PAHs interacted with GSTT1, GSTM1, GSTP1, and GSTA1 polymorphisms to increase breast cancer risk.

Question

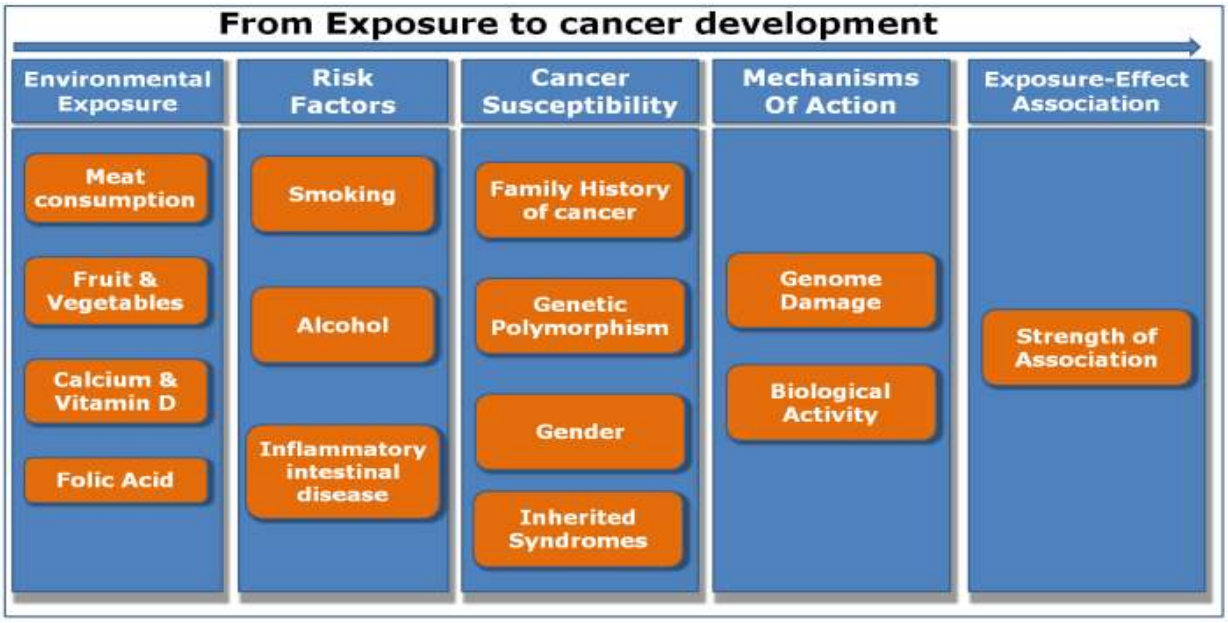
What is your level of confidence in scientists' ability to predict the effect of environmental exposure to PHAs on breast cancer risk?

COLORECTAL TUMORS

- Adenocarcinoma (95%) of cases
  - Adenocarcinoma
  - Adenocarcinoma in adenomatous polyp
  - Adenocarcinoma in adenomatous polyposis coli
  - Adenocarcinoma in villous adenoma
- Mucinous adenocarcinoma
- Signet-ring cell carcinoma
- Lymphoma

Localization

- Right or proximal colon
  - Cecum
  - Ascending colon
  - Hepatic flexure
  - Proximal transverse colon (approximately the first two-thirds of the transverse)
- Left or distal colon
  - The last third of the transverse
  - Splenic flexure
  - Descending colon
  - Sigmoid colon
- Rectosigmoid
- Rectum



RISK FACTORS (are valid for ALL exposures)

SMOKING

CRC risk is increased in smokers.

ALCOHOL

A high alcohol intake is associated with an increased risk of colon cancer (RR=1.50 (1.25-1.79).

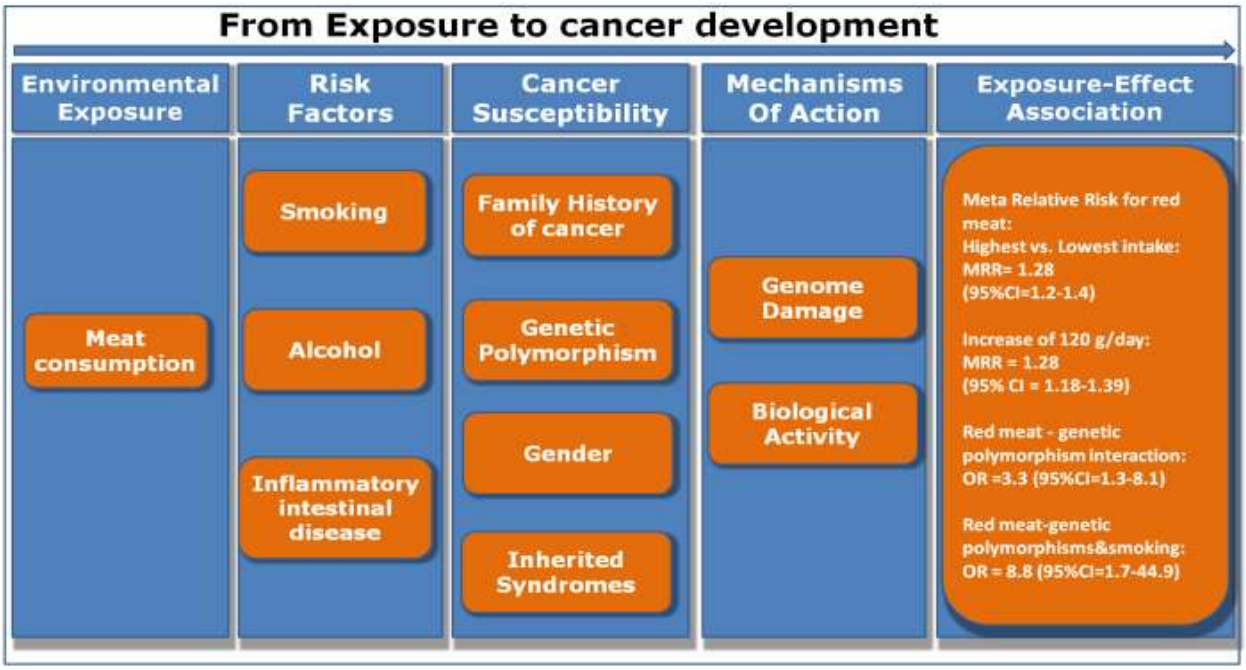
INFLAMMATORY INTESTINAL DISEASE
Risk of CRC doubles among patients with ulcerative colitis or Crohn's disease.

CANCER SUSCEPTIBILITY (are valid for ALL exposures)
FAMILY HISTORY OF CANCER
Family history of colon cancer in first-degree relatives
at least one relative: MOR=2.24 (2.06-2.43)
at least two relatives: MOR=3.97 (2.60-6.06)

GENDER
Incidence is higher in males than females

INHERITED SYNDROMES
Familial adenomatous polyposis (FAP) and hereditary non polyposis colorectal cancer (HNPCC) associated with lifetime increased risk of CRC.

COLON – MEAT CONSUMPTION



GENETIC POLYMORPHISMS
CYP2E1, GSTA1, CYP1A2, NAT2 polymorphisms play an effect on susceptibility to CRC (OR=3.3; 95%CI:1.3-8.1)

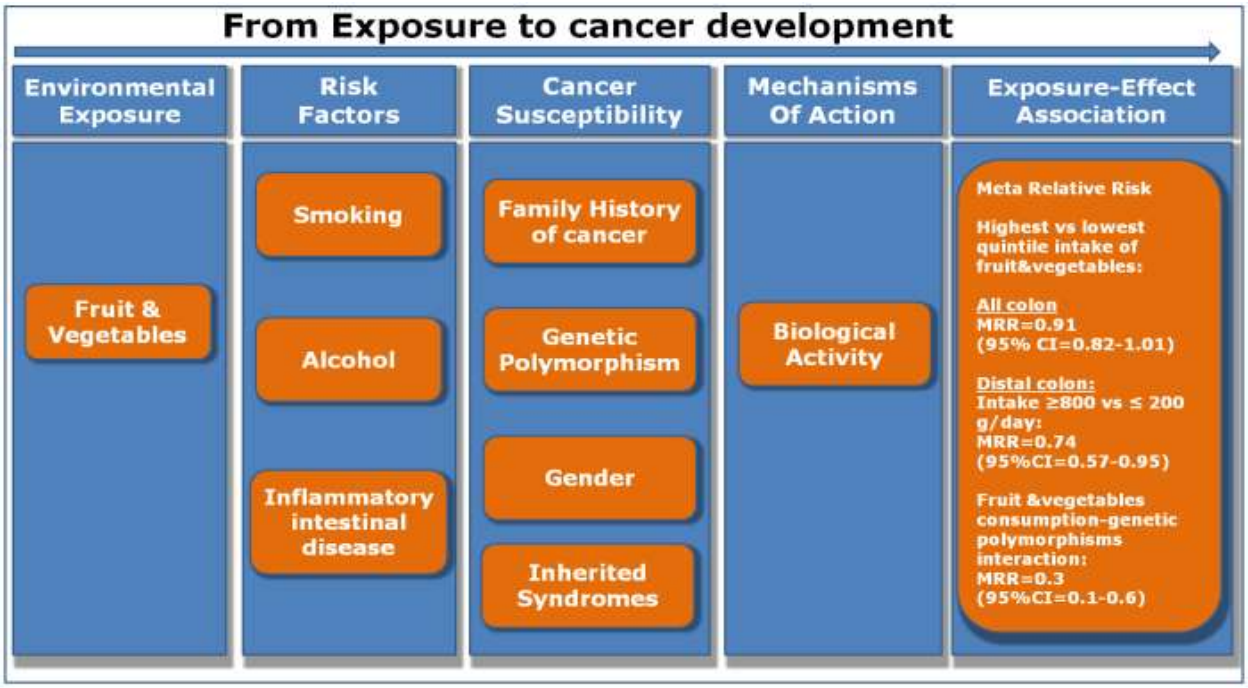
MECHANISMS OF ACTION
GENOME DAMAGE
Chemical compounds produced during cooking can bind to macromolecules and DNA.

BIOLOGICAL ACTIVITY
Heterocyclic amines produced during cooking of red meat are suggested to cause CRC.

Question

What is your level of confidence in scientists' ability to predict the impact of red meat consumption on CRC risk?

COLON – FRUIT AND VEGETABLES



GENETIC POLYMORPHYSMS

CYP2E1, CYP1A2, NAT2, GSTM1 and GSTT1 polymorphisms interact with high fruit and vegetable consumption to decrease colon cancer risk.

MECHANISMS OF ACTION

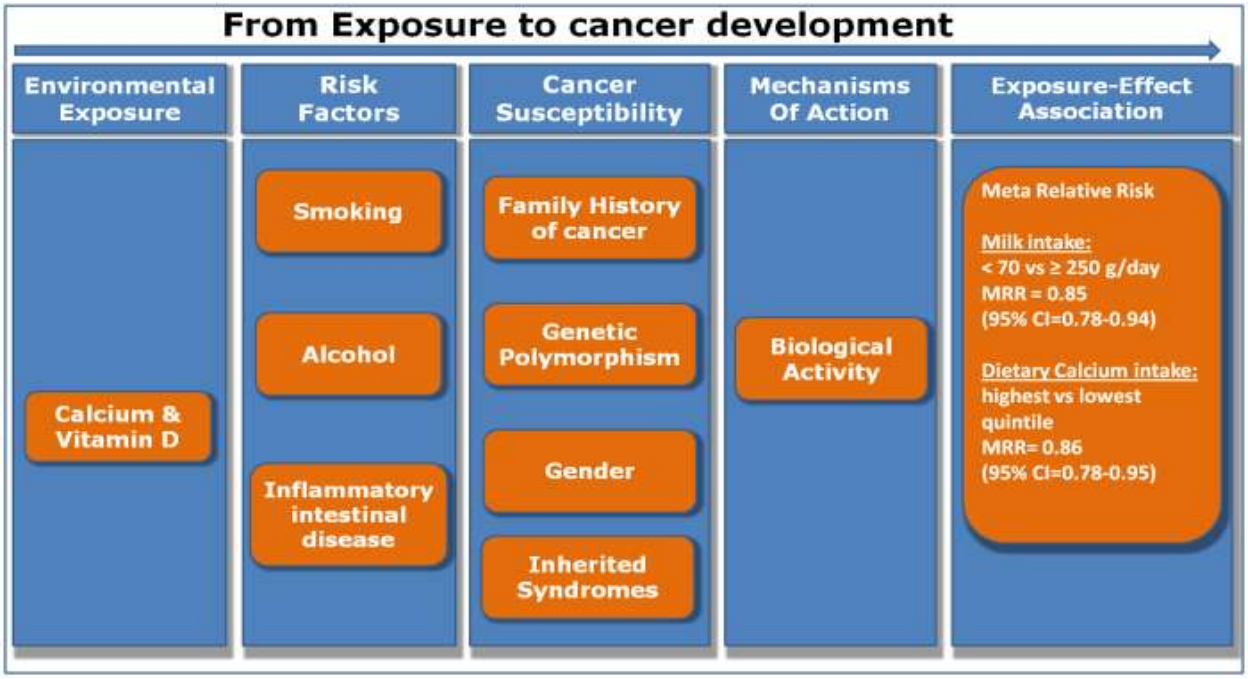
BIOLOGICAL ACTIVITY

Phytochemicals in fruits and vegetables have antioxidant activities. Additive and synergistic effects of phytochemicals in fruits and vegetables are responsible for anticancer activity. The benefit of a diet rich in fruits and vegetables is attributed to phytochemicals present in whole foods.

Question

What is your level of confidence in scientists' ability to predict the role of fruit and vegetables intake on CRC risk?

COLON – CALCIUM AND VITAMIN D



GENETIC POLYMORPHYSMS

CYP2E1, CYP1A2, NAT2, GSTM1 and GSTT1 polymorphisms interact with high fruit and vegetable consumption to decrease colon cancer risk.

MECHANISMS OF ACTION

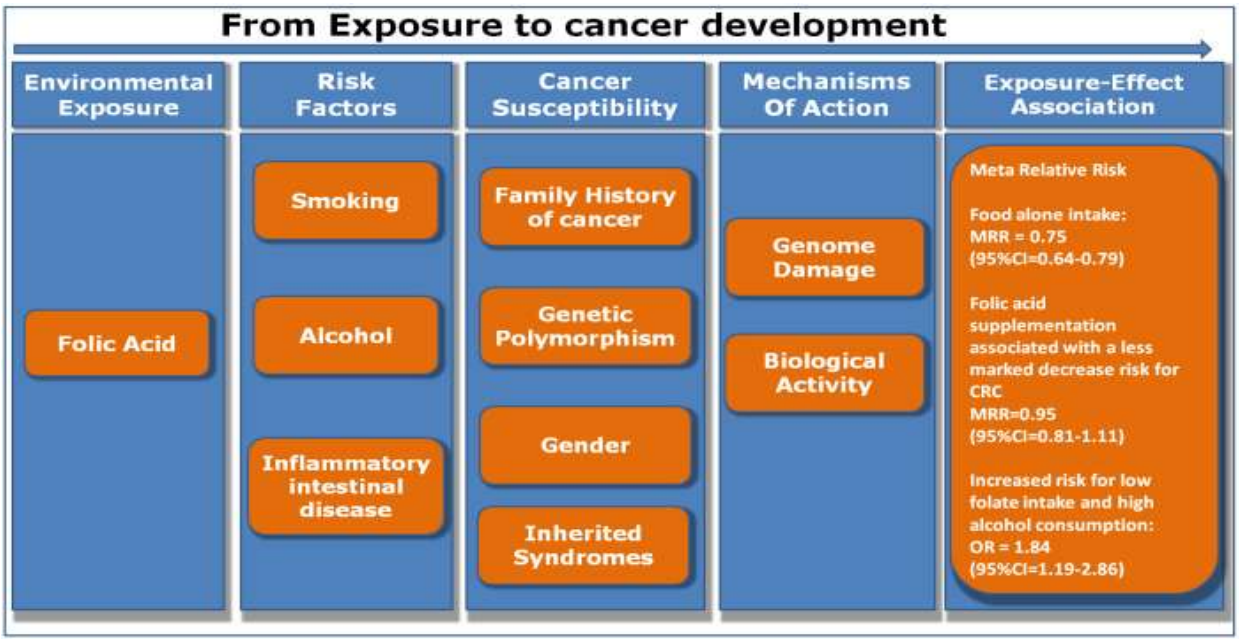
BIOLOGICAL ACTIVITY

Calcium and vitamin D are thought to reduce risk by decreasing cell proliferation or promoting cell differentiation.

Question

What is your level of confidence in scientists' ability to predict the role of calcium and or Vitamin D intake on CRC risk?

COLON – FOLIC ACID



GENETIC POLYMORPHYSMS
Reduced risk in homozygotes with a variant form of the enzyme that regulates the conversion of folate.

MECHANISMS OF ACTION
GENOME DAMAGE
A low folate intake is associated with an increased frequency of chromosome breaks and micronucleated cells.

BIOLOGICAL ACTIVITY
Folate is a critical cofactor in biological methylation and nucleotide synthesis: a low folate level increases DNA methylation.

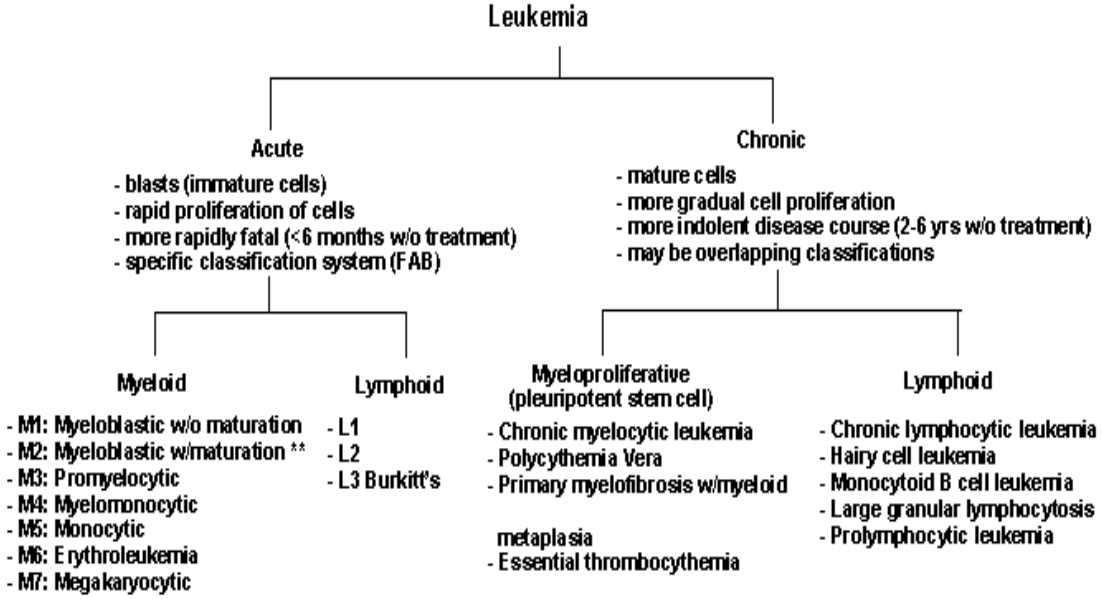
Question

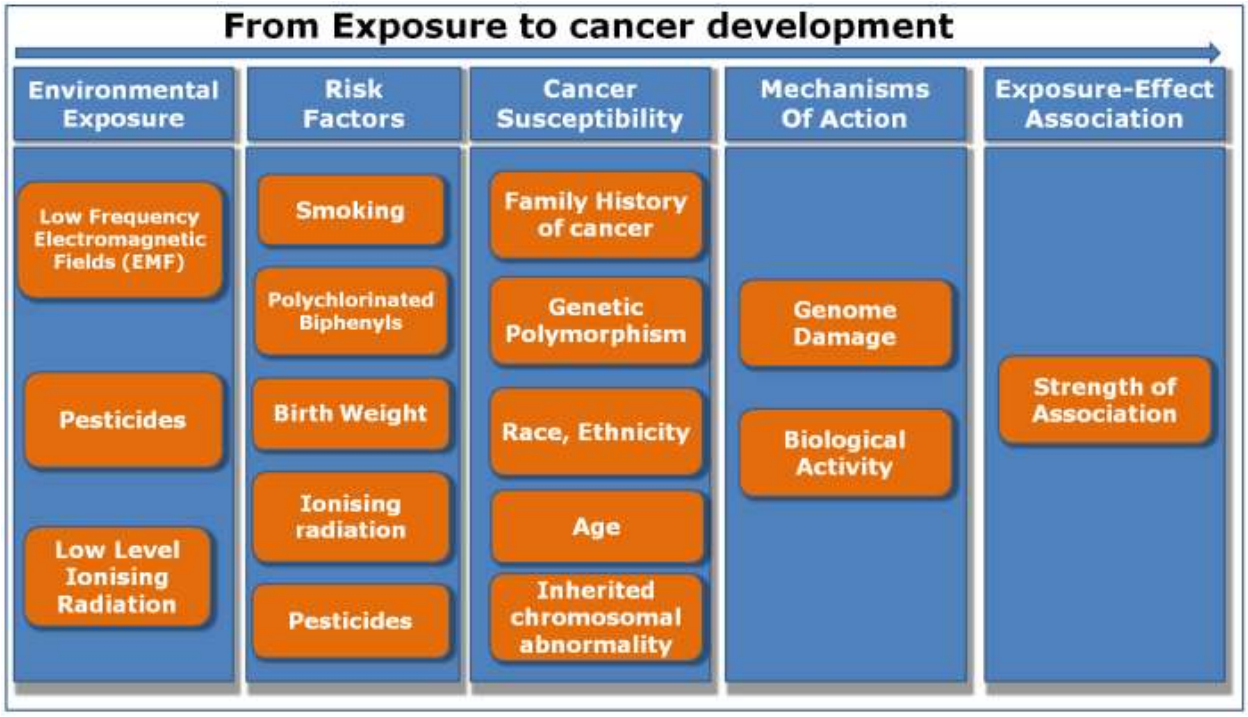
What is your level of confidence in scientists' ability to predict the role of folic acid supplementation on CRC risk?

What is your level of confidence in scientists' ability to explain the debate on the paradoxical role of folic acid intake on CRC risk (supplementation appears to be associated with a less marked decrease of risk for CRC)?

LEUKEMIA

A progressive, malignant disease of the blood-forming organs. It is characterized by overproduction of white blood cells and their precursors in the blood and bone marrow.
Leukaemia is classified according to degree of cell differentiation as **acute** or **chronic,** and according to predominant type of cell involved as **myelogenous** or **lymphocytic**.





RISK FACTORS (apply for ALL exposures)

SMOKING

Cigarette smoke contains leukemia-causing chemicals (e.g., benzene). One in four cases of acute myelogenous leukemia (AML) is attributed to cigarette smoking.

POLYCHLORINATED BIPHENYLS
PCBs may represent a risk factor for childhood leukemia (they are probable human carcinogens and cause perturbations of the immune system).

BIRTH WEIGHT
High birth weight may be associated with an increased risk of overall leukemia and acute lymphocytic leukemia (ALL).

IONIZING RADIATION
People who have been exposed to high doses of ionizing radiation (i.e., atomic bomb survivors) have a high risk of chronic myelogenous leukemia (CML).

P*ESTICIDES*
Increased risks have been reported in workers exposed to herbicides, and pesticides, particularly for chronic lymphocytic leukemia (CLL).

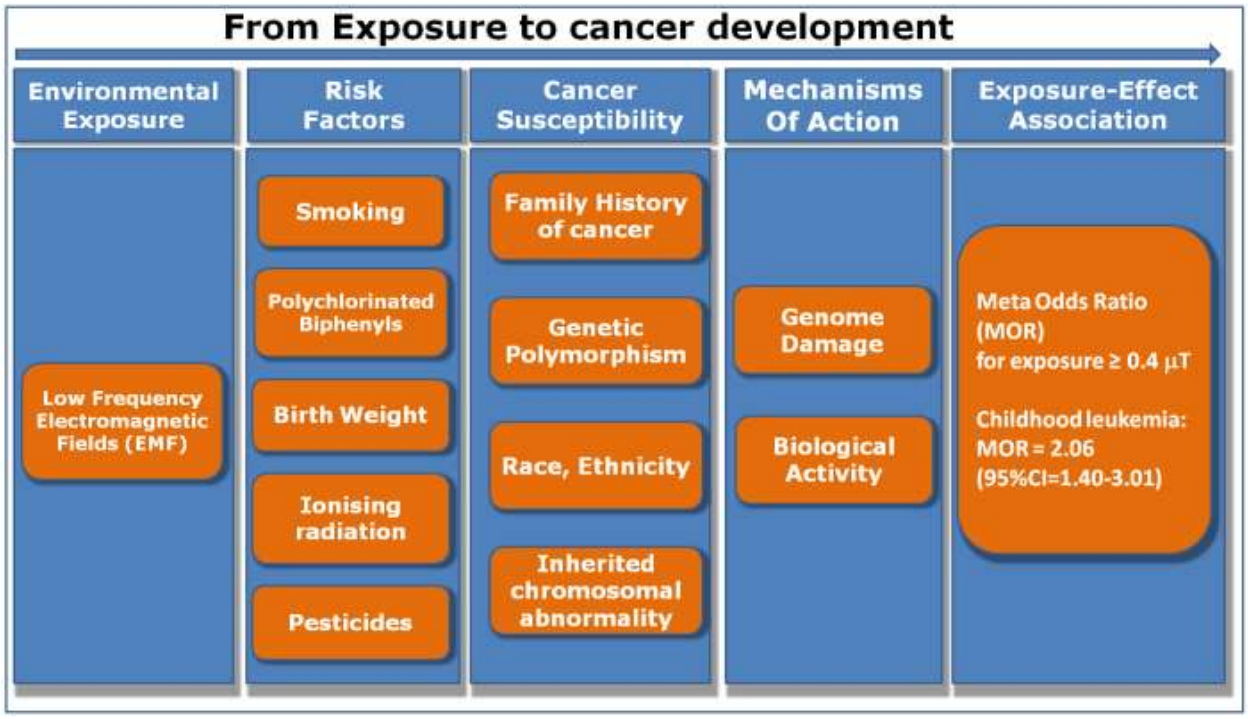
CANCER SUSCEPTIBILITY (apply for ALL exposures)
FAMILY HISTORY OF CANCER
First-degree relatives of chronic lymphocytic leucemia (CLL) patients have an increased risk for this cancer.

GENETIC POLYMORPHYSMS
Increased risk in children carrying the the CYP1A1m1 and CYP1a1m2 mutations exposed to indoor insecticides.
Several low-penetrance genes (CYP, NQO1, GSTT1, GSTM1, GSTP1, MTHFR, TYMS, SHMT1, MTRR, XPD, XPG, RAD51, XRCC1, XRCC3, CHEK2, ATM) may account for the risk of leukaemia via gene-environment interaction.

RACE, ETNICITY
Rates of leukemia (e.g., CLL) are elevated in some Jewish populations and low in Asian populations.

INHERITED CHROMOSOMAL ABNORMALITY
Children with Down's syndrome have a higher risk of leukemia. Other inherited disorders (Fanconi's anemia, Bloom's syndrome, and ataxia telangiectasia) have an increased risk for leukemia.

LEUKEMIA – ELECTROMAGNETIC FIELDS (EMF)



MECHANISMS OF ACTION

GENOME DAMAGE

EMF do not have sufficient energy to affect DNA molecules, but even weak electric and magnetic fields can cause changes in charge distribution that trigger large structural changes in proteins.

BIOLOGICAL ACTIVITY

Weak EMF can control and amplify biological processes through their effects on charge distribution.

Questions

What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to residential low frequency electromagnetic fields and the risk of leukaemia in children?

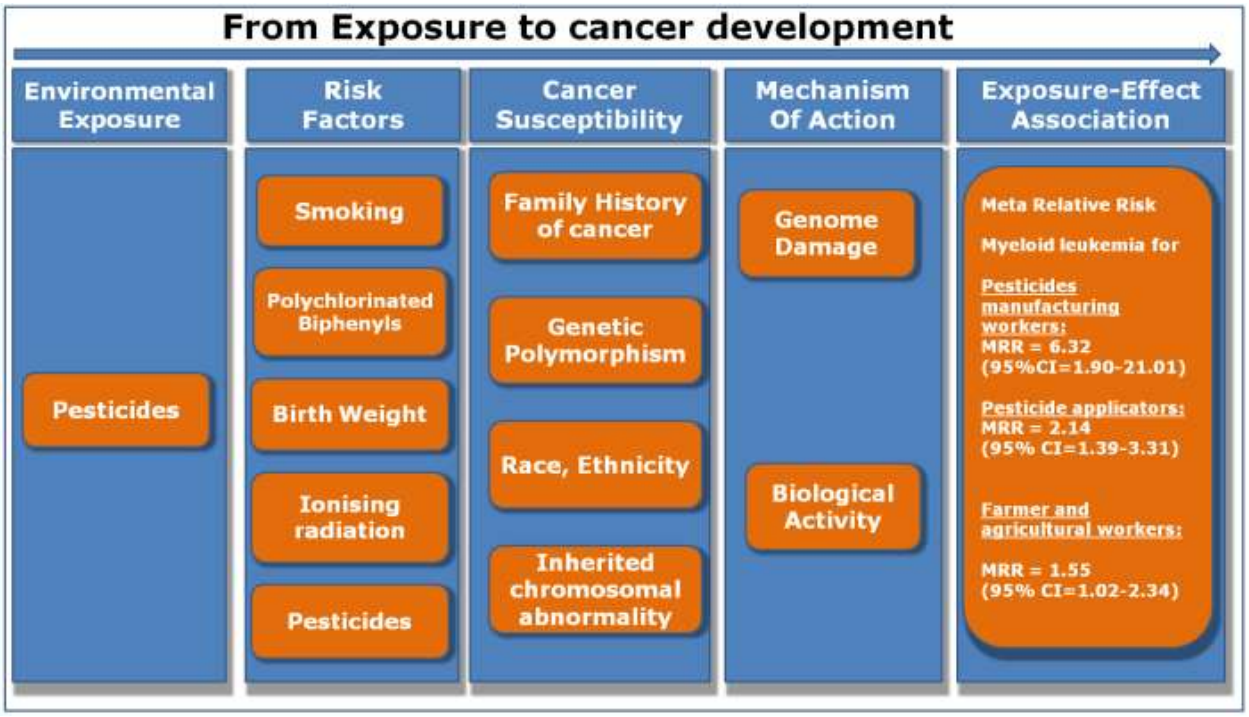
What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to residential electromagnetic fields on leukaemia risk?

Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle) to reduce EMF exposure?

In favor ☐ Against ☐

If you have any specific policy actions in mind, please specify them here:

LEUKEMIA - PESTICIDES



MECHANISMS OF ACTION

GENOME DAMAGE

Chromosome aberrations and increased frequency of micronuclei have been detected in the majority of studies, mitotic arrest, clastogens, aneugens, some pesticides cause disturbances of mitotic spyndle

BIOLOGICAL ACTIVITY

Translocations or clonotypic gene fusion sequences match that of later leukemic blasts in blood spots (Guthrie card); some pesticides are xenoestrogens, ROS production.

Questions

What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to pesticides and the risk of leukaemia?

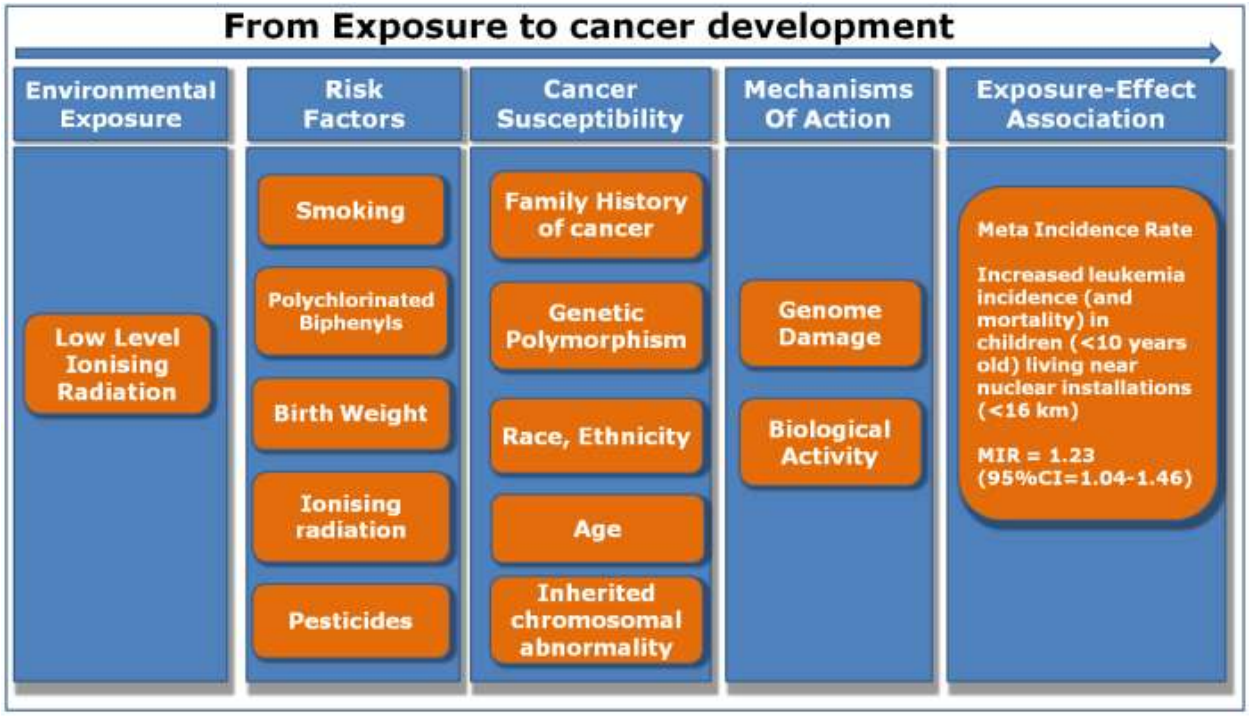
What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to pesticides on leukaemia risk?

Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle) to reduce pesticides exposure?

In favor ☐ Against ☐

If you have any specific policy actions in mind, please specify them here:

LEUKEMIA – LOW LEVEL IONISING RADIATION



MECHANISMS OF ACTION

GENOME DAMAGE

Chromosome aberrations and increased frequency of micronuclei have been detected in the majority of studies.

BIOLOGICAL ACTIVITY

Translocations or clonotypic gene fusion sequences match that of later leukemic blasts in blood spots (Guthrie card); ROS production; damage DNA, RNA, proteins by breaking chemical bonds and cross-linking between macromolecules, inducing methylation disturbances.

Questions

What is your level of confidence in the current scientists' ability to predict the impact of environmental exposure to low level ionising radiation and the risk of leukaemia?

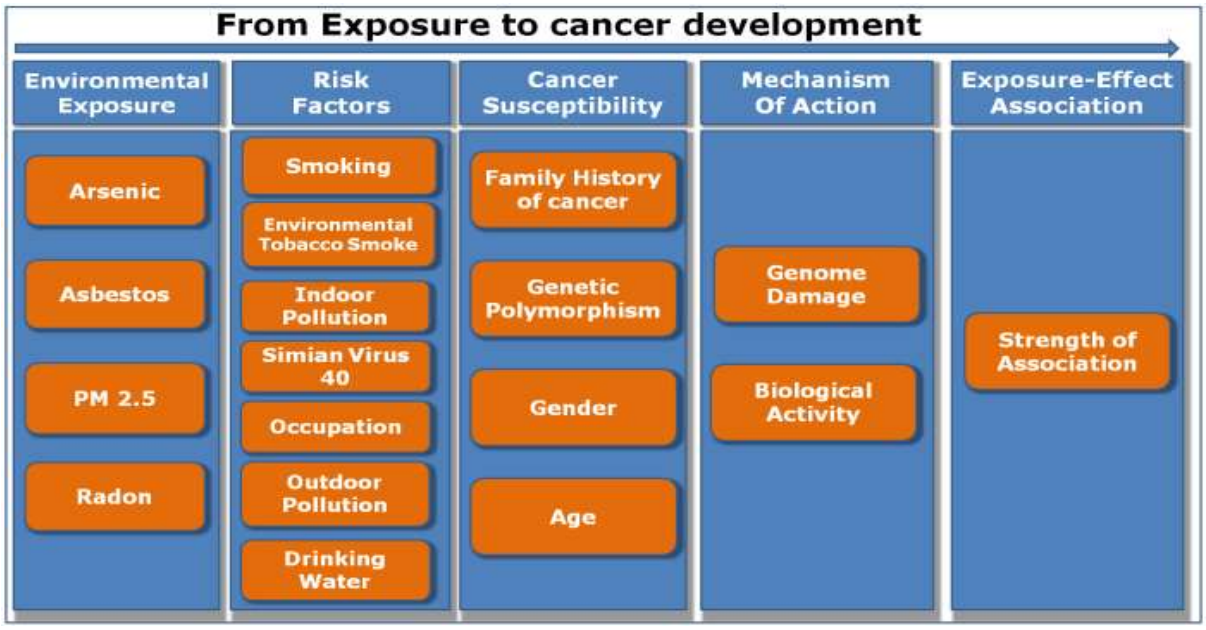
What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and/or early childhood exposure to low level ionising radiation on childhood leukaemia risk?

Given the available scientific evidence, would you be in favour or against preventive measures (precautionary principle) to reduce exposure to ionising radiation?

In favor ☐ Against ☐

If you have any specific policy actions in mind, please specify them here:

LUNG MESOTHELIOMA



From a clinical and prognostic standpoint, lung carcinomas are broadly divided into non small cell carcinoma (NSCLC) and small cell carcinoma (SCLC), accounting for 20-25% of all lung carcinomas. NSCLCs traditionally include three major types: adenocarcinoma, squamous cell carcinoma (SSC) and large cell carcinoma, but in the broadest sense may include any epithelial tumor that lacks a small cell component.

TYPES OF MALIGNANT PLEURAL MESOTHELIOMA

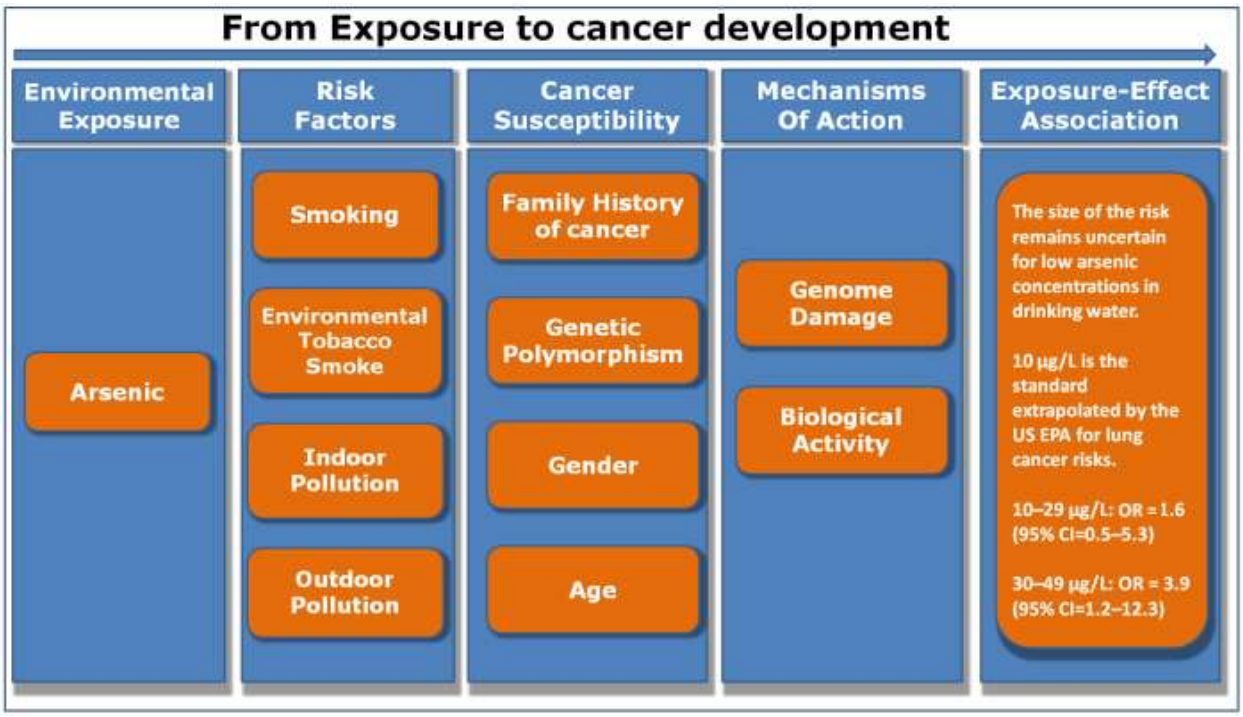
- Epithelial
- Sarcomatoid
- Desmoplastic
- Biphasic or mixed

Approximately 60% of MPM cases have epithelial histology, 30% biphasic or mixed, and the remaining 10% sarcomatoid. Biphasic tumors must have both epithelioid and sarcomatoid components, with the minor component representing at least 10% of the tumor area.

TYPES OF LUNG TUMORS

- Malignant epithelial lung tumors
  - Squamous cell carcinoma
  - Small cell carcinoma
  - Adenocarcinoma
  - Large cell carcinoma
  - Adenosquamous carcinoma
  - Sarcomatoid carcinoma
  - Carcinoid tumour
  - Salivary Gland Tumors
  - Preinvasive lesions
  - Mesenchymal tumours
- Benign epithelial tumours
- Lymphoproliferative tumours
- Metastatic tumours
- Others

LUNG – ARSENIC



RISK FACTORS

SMOKING

Smoking is the major risk factor for lung cancer.
Arsenic and cigarette smoke synergistically increase DNA oxidation in the lung.

ENVIRONMENTAL TOBACCO SMOKE

Exposure to environmental tobacco smoke is associated with lung cancer development:
MRR=1.36 (95%CI:1.02-1.82).

INDOOR POLLUTION

Lung cancer may be associated with indoor pollution from heating an cooking with solid fuels.
Indoor radon is associated with an increased lung cancer risk.

OUTDOOR POLLUTION

Combustion products from fossil fuels containing carcinogenic PAHs (e.g., diesel exhaust).
The component with the greatest public impact is probably $PM_{2.5}$: RR increase range between 15% and 21% for a 10 µg/m^3 increase in $PM_{2.5}$ air level.
Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6)

CANCER SUSCEPTIBILITY

FAMILY HISTORY OF CANCER

Systematic reviews have shown a relationship between family history and lung cancer risk (Meta RR = 1.51, 95%CI =1.11–2.06). Risk appears to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members.

GENETIC POLYMORPHISMS

GSTM1 may have an important role in As methylation capacity and body retention.
A susceptibility locus for lung cancer: nicotinic acetylcholine receptor subunit genes
Carriers of the GSTM1 null genotype have an increased lung cancer risk: MOR=1.64 (95%CI=1.25-2.14); carriers of the GSTT1 null genotype: MOR= 1.49 (95%CI=1.17-1.89).

GENDER
Female smokers are at higher risk for lung cancer than male smokers. Endocrine factors may play a role in adenocarcinoma of the lung in women.

AGE
Exposure in utero and early childhood to carcinogenic agents may lead to increased lung cancer risk later in life.

MECHANISMS OF ACTION
GENOME DAMAGE
Arsenic metabolites methylarsonic acid (MMA) and dimethylarsinic acid (DMA) are cytotoxic and genotoxic in cell lines (chromosomal abnormalities, oxidative stress); MMA is metabolised to DMA and both compounds are classified as "possibly carcinogenic to humans" (Group 2B).

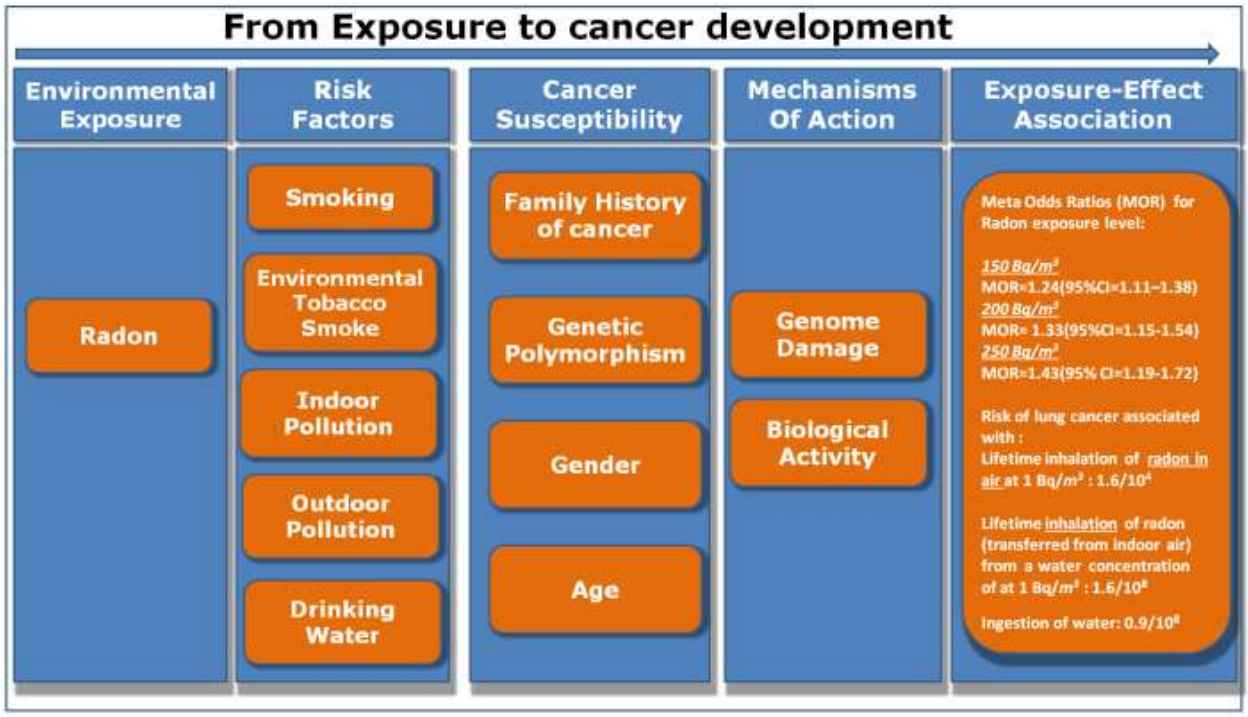
BIOLOGICAL ACTIVITY
Arsenic causes oxidative DNA damage, genomic instability, aneuploidy, gene amplifi cation, epigenetic effects. DNA methylation of specific genes are associated with risk factors and gender; DNA-repair inhibition leads to mutagenesis.

Questions

What is your level of confidence in scientists' ability to predict the impact of environmental exposure to arsenic in drinking water on lung cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of a synergistic effect between arsenic in drinking water and smoking on lung cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and early childhood exposure to arsenic in drinking water on lung cancer risk?



RISK FACTORS

SMOKING

Smoking is the major risk factor for lung cancer.

Smoking exerts a supra additive effect on Radon-induced lung cancer risk.

ENVIRONMENTAL TOBACCO SMOKE

Exposure to environmental tobacco smoke is associated with lung cancer development: MRR=1.36 (95%CI:1.02-1.82).

INDOOR POLLUTION

Lung cancer may be associated with indoor pollution from heating and cooking with solid fuels.

OUTDOOR POLLUTION

Combustion products from fossil fuels contains carcinogenic PAHs.The component with the greatest public impact is probably $PM_{2.5}$: RR increase range between 15% and 21% for a 10 µg/m^3 increase in PM2.5 air level. Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6)

DRINKING WATER

Ingesting drinking water with high concentrations of arsenic is associated with lung cancer risk.

CANCER SUSCEPTIBILITY

FAMILY HISTORY OF CANCER

Systematic reviews have shown a relationship between family history and lung cancer risk (Meta RR = 1.51, 95%CI =1.11–2.06). Risk appears to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members.

GENETIC POLYMORPHISMS
A susceptibility locus for lung cancer: nicotinic acetylcholine receptor subunit genes.
Carriers of the GSTM1 null genotype have an increased lung cancer risk. MOR=1.64 (95%CI=1.25-2.14); carriers of the GSTT1 null genotype: MOR= 1.49 (95%CI=1.17-1.89)

GENDER
Female smokers are at higher risk for lung cancer than male smokers.
Endocrine factors may play a role in adenocarcinoma of the lung in women.

AGE
Exposure in utero and early childhood to carcinogenic agents may lead to increased lung cancer risk.
later in life

MECHANISMS OF ACTION
DNA DAMAGE
Radon induces chromosome damage at very low doses (dicentrics, acentric fragments and centric rings); increases the frequency of micronuclei in in vitro exposed human lymphocytes.

BIOLOGICAL ACTIVITY
Radon alpha particles create dense ionization: cells nucleus are severely injured by particles track. Injuries include gene deletions, rearrangements, amplifications, persistant genomic instability, mutations in oncogenes, loss of function in tumor suppressors, all contributing to malignant transformation.

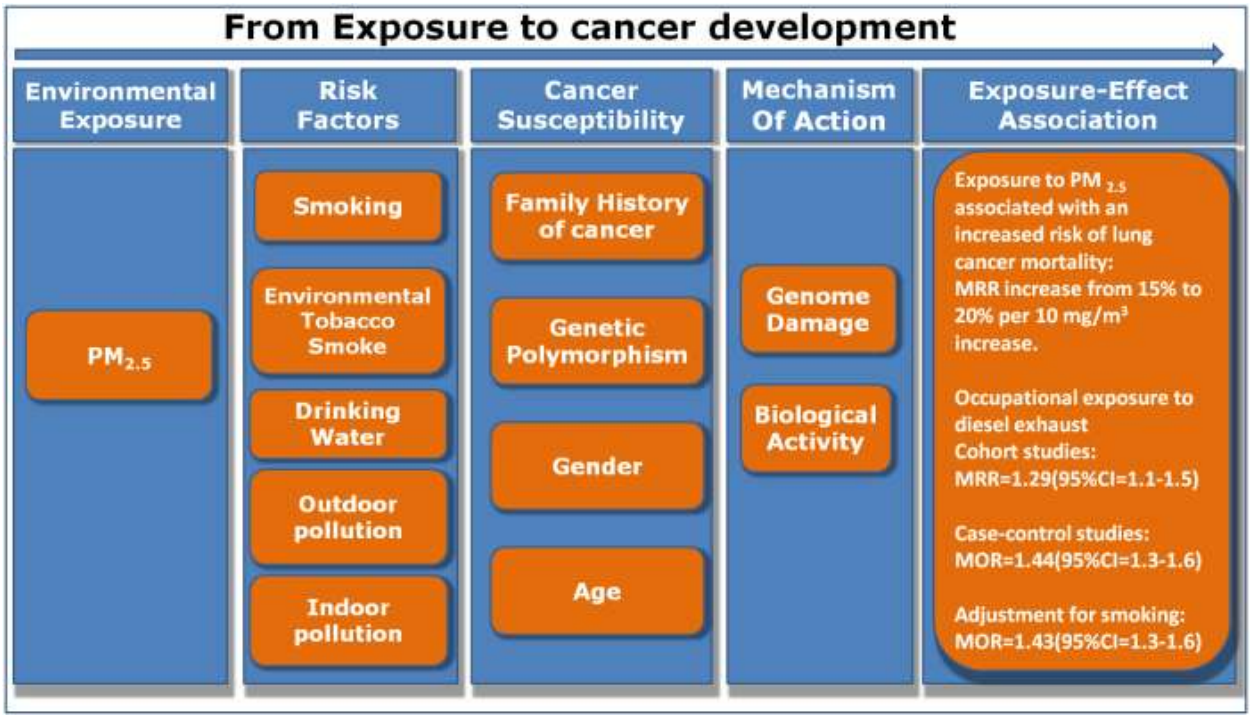
Questions

What is your level of confidence in scientists' ability to predict the impact of environmental exposure to Radon on lung cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of a synergistic effect between Radon exposure and smoking on lung cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of in utero and early childhood exposure to Radon on lung cancer risk?

LUNG – PM 2.5



RISK FACTORS

SMOKING

Smoking is the major risk factor for lung cancer.

ENVIRONMENTAL TOBACCO SMOKE

Exposure to environmental tobacco smoke is associated with lung cancer development: MRR=1.36 (95%CI:1.02-1.82).

DRINKING WATER

Ingesting drinking water with high concentrations of arsenic is associated with lung cancer risk.

OUTDOOR POLLUTION

Combustion products from fossil fuels contains carcinogenic PAHs.
Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6).

INDOOR POLLUTION

Lung cancer may be associated with indoor pollution from heating and cooking with solid fuels
Indoor radon is associated with an increased lung cancer risk.

CANCER SUSCEPTIBILITY

FAMILY HISTORY OF CANCER

Systematic reviews have shown a relationship between family history and lung cancer risk
(Meta RR = 1.51, 95%CI =1.11–2.06). Risk appears to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members.

GENETIC POLYMORPHISMS

Air pollutants (e.g., PAHs) require metabolic activation to exhert genotoxicity and to be excreted: phase I and phase II metabolic genes polymorphism may increase cancer risk.
Carriers of the GSTM1 null genotype have an increased lung cancer risk. MOR=1.64 (95%CI=1.25-2.14); carriers of the GSTT1 null genotype: MOR= 1.49 (95%CI=1.17-1.89).

GENDER
Female smokers are at higher risk for lung cancer than male smokers.
Endocrine factors may play a role in adenocarcinoma of the lung in women.

AGE
Exposure in utero and early childhood may increase the risk of lung cancer development later in life.

MECHANISMS OF ACTION
DNA DAMAGE
Indoor and outdoor agents have genotoxic properties and induce oxidative stress.

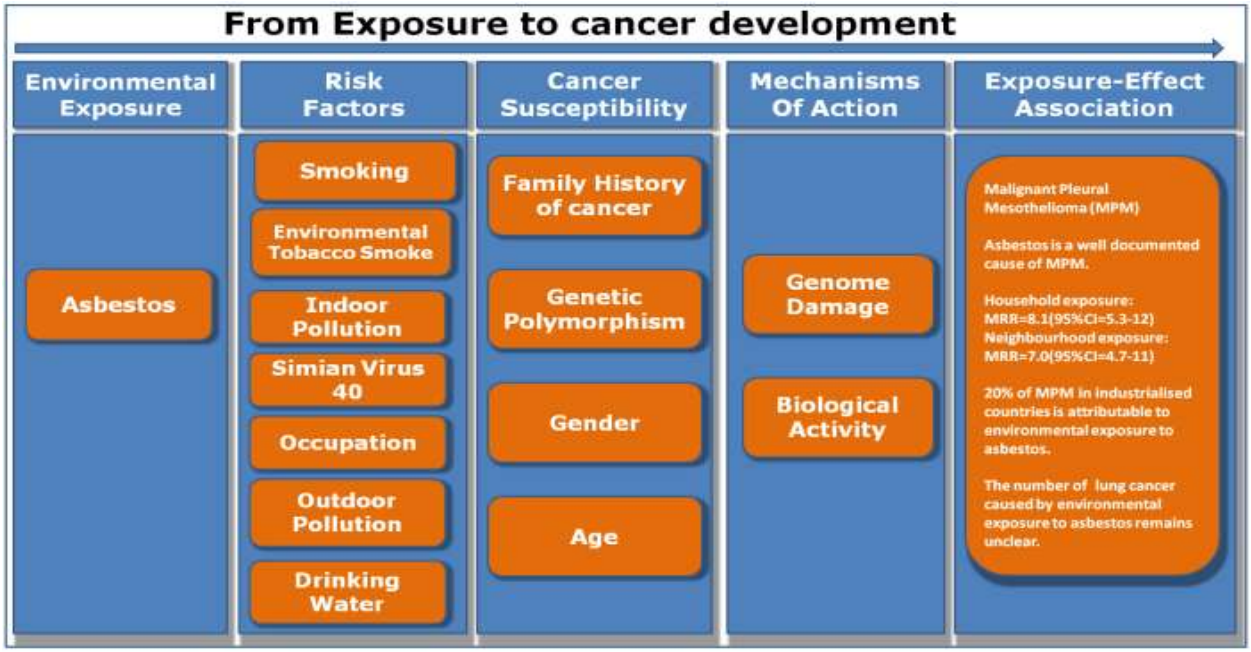
BIOLOGICAL ACTIVITY
Fuel combustion products contain carcinogens. It is not clear whether PM2.5 possesses carcinogenic properties beyond those of the known chemical carcinogens which it contains (PAH, Cr, Ni, and As). Coal combustion increases indoor levels of PAHs, benzene, arsenic, and formaldehyde. Peanut oil, when heated, releases mutagenic compounds and soybean, sunflower, rapeseed oil, and lard have genotoxic properties and induce oxidative stress.

Questions

What is your level of confidence in scientists' ability to predict the impact of environmental exposure to PM2.5 on lung cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of indoor heating and cooking with solid fuels on lung cancer risk?

LUNG - ASBESTOS



RISK FACTORS

SMOKING

Smoking does not increase the risk of MPM, but is the major risk factor for lung cancer.
There is a synergistic effect between asbestos and tobacco smoking in lung cancer risk.
The excess relative risk of lung cancer from asbestos exposure is about three times higher in non-smokers than in smokers.

ENVIRONMENTAL TOBACCO SMOKE

Exposure to environmental tobacco smoke is associated with lung cancer development: MRR=1.36 (95%CI:1.02-1.82).

INDOOR POLLUTION

Lung cancer may be associated with indoor pollution from heating and cooking with solid fuels.
Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6).

SIMIAN VIRUS 40 (SV40)

SV40 was found in 1960 in kidney cells of rhesus macaque monkey that were used in the production of the polio vaccines. Infants vaccinated with the SV40 contaminated poliovirus vaccine may have increased risk of mesothelioma and other cancers. The scientific evidence is insufficient to prove or disprove a causal role of poliovirus vaccine contaminated with SV40.

OCCUPATION

Working with asbestos (occupational exposure) is the major risk factor for MPM. Lung cancer risk increases with increasing duration of exposure to asbestos.

OUTDOOR POLLUTION

Outdoor air pollution is suspected of increasing the risk of lung cancer. The component with the greatest public impact is probably PM2.5: RR increase range between 15% and 21% for a 10 µg/m3 increase in PM2.5 air level. Occupational exposure to diesel exhaust increases lung cancer risk: MOR=1.43 (95%CI=1.3-1.6)

DRINKING WATER
Ingesting drinking water with high concentrations of arsenic is associated with lung cancer risk.

CANCER SUSCEPTIBILITY
FAMILY HISTORY OF CANCER
Systematic reviews have shown a relationship between family history and lung cancer risk (MRR = 1.51, 95%CI =1.11–2.06). Risk appears to be greater in relatives of cases diagnosed at a young age and in those with multiple affected family members.

GENETIC POLYMORPHISMS
The polymorphic metabolic/oxidative enzyme myeloperoxidase (MPO) genotypes modify the effect of asbestos exposure on lung cancer risk: OR=1.72 (95% CI; 1.09-2.66)
The polymorphism of other genes are associated to an increased risk of MPM
GSTM1: OR= 1.69 (95%CI =1.04-2.74), MnSOD: OR= 3.07. 95% CI = 1.55-6.05), XRCC1-399Q: 2.38 (95% CI=0.82-6.94)

GENDER
Female smokers are at higher risk for lung cancer than male smokers

AGE
Exposure in utero and early childhood to carcinogenic agents may lead to increased lung cancer risk later in life

MECHANISMS OF ACTION
GENOME DAMAGE
Chromosomes are damaged by asbestos when cells divide. Mitochondria are targets of asbestos-induced DNA damage and apoptosis via an oxidant-related mechanism. Impaired fibre clearance leads to macrophage activation, infl ammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signalling pathways, resistance to apoptosis

BIOLOGICAL ACTIVITY
Asbestos act as a carcinogen by generating free radicals and reactive oxygen species, inducing tissue injury and subsequent cellular growth. Asbestos fibers may concentrate chemical carcinogens including the components of cigarette smoke. Asbestos enhances the mutagenicity of tobacco carcinogens.

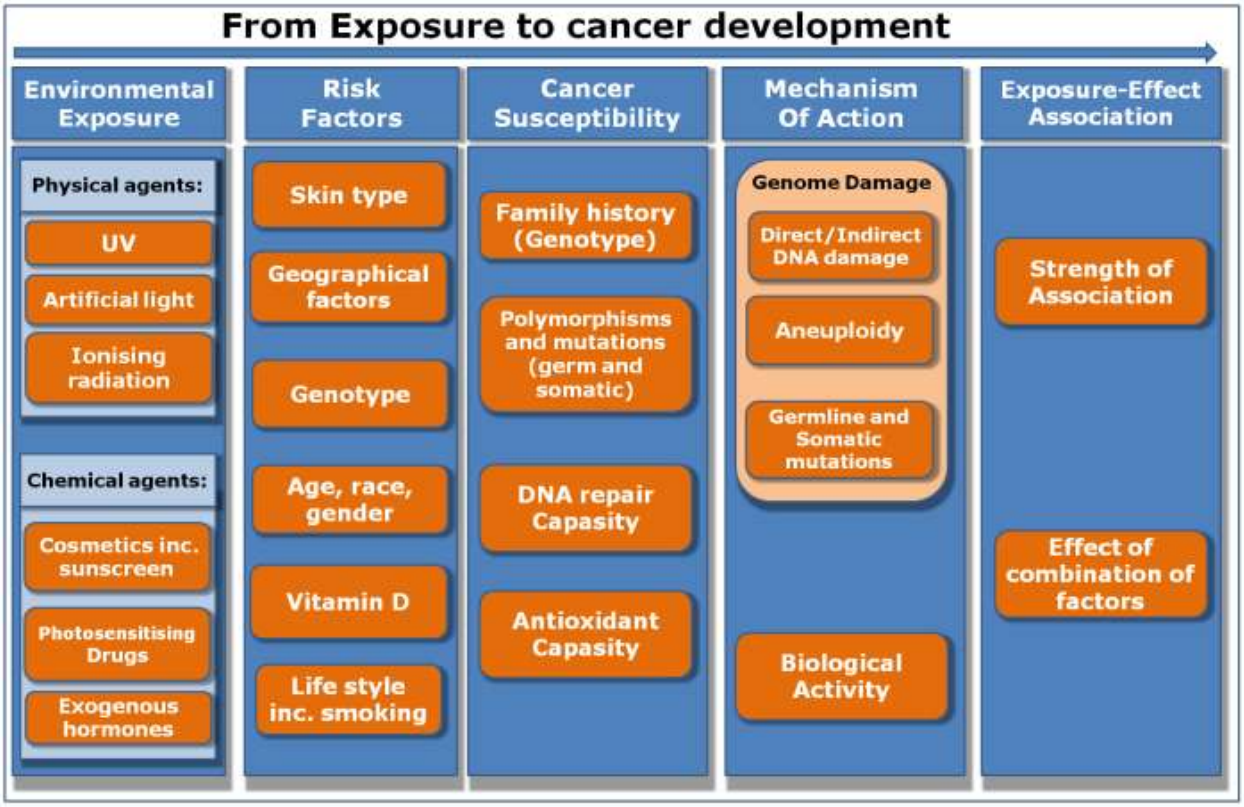
Questions

What is your level of confidence in scientists' ability to predict the impact of environmental exposure to asbestos on MPM risk?

What is your level of confidence in scientists' ability to predict the impact of environmental exposure to asbestos on lung cancer risk?

What is your level of confidence in scientists' ability to assess the role and the magnitude of exposure to Simiam virus vaccination on MPM risk?

MELANOMA



Malignant tumor of melanocytes accounts for 90% of skin cancer mortality arises from dendritic melanocytes in the skin, (eyes, mucosa, meninges). Incidence of melanoma is dramatically increasing. While in US the lifetime risk of melanoma in 1935 was 1 in 1,500 persons, in 1960, 1 in 600 persons, lifetime risk of melanoma in 2000 was 1 in 75 persons.

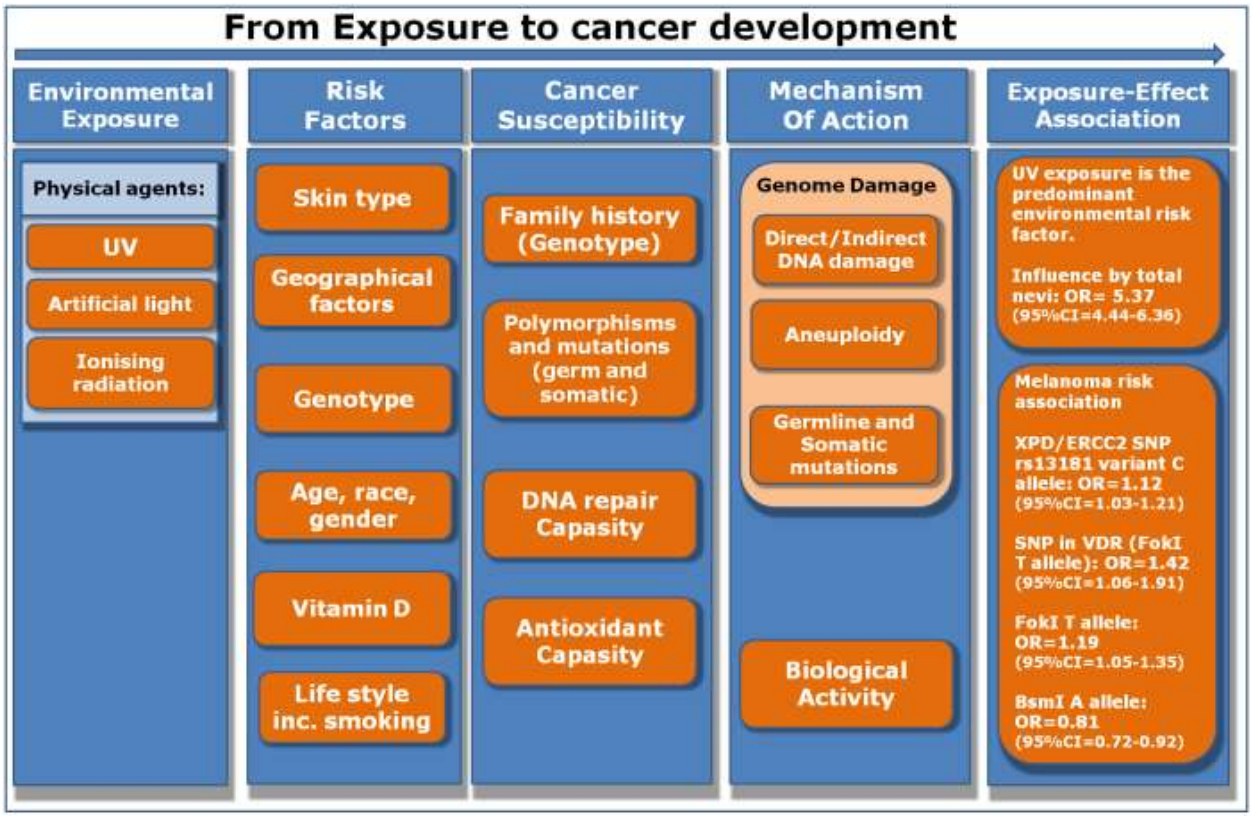
Types of Melanoma:

- Superficial spreading melanoma (about 70% of diagnosed cases) – any age (middle aged)
- Nodular melanoma (about 15% of diagnosed cases) – middle aged
- Lentigo maligma melanoma (about 10% of diagnosed cases) – middle aged, elderly
- Acral lentigous melanoma (about 5% of diagnosed cases) – Asian and dark skin
- Melanoma of the skin - cutaneous.

Melanoma can occur anywhere in the body, including in the internal organs.

MELANOMA - PHYSICAL AGENTS

Physical agents: (UV, artificial light, ionising radiation): Among the risk factor the sun-exposure (intermittant exposure, exposure in childhood) is one of the major risk factors in occurrence of melanoma. High exposure in the childhood combined with high exposure in adult life give a high risk of melanoma.



RISK FACTORS

SKIN TYPE

Malignant melanoma mainly afflicts people with white skin (Caucasian population). Risk of melanoma depends on skin type. Particularly dysplastic nevi confer much higher risks than most pigmentary characteristics.

GEOGRAPHICAL FACTORS

Sun exposure plays a primary and supporting role in most melanoma tumors. UV radiation exposure is the predominant environmental risk factor for melanoma. Melanoma incidence varies across countries, depending on differences in UV radiation in different geographical regions.

GENOTYPE

Approximately 10% of melanoma is inherited (Familial). About 40 percent of familial melanoma is associated with chromosome 9p. There are geographical variation in the penetrance of the melanoma susceptibility genes CDK4 and CDKN2A mutations.

RACE, GENDER AND AGE

Malignant melanoma mainly afflicts Caucasian population. Among cases aged 15-30 years, females have a higher melanoma risk; after age 30, incidence is higher among males. Generally older age and male gender are associated with prognostically unfavorable primary cutaneous melanoma.

VITAMIN D
Indoor solar UVA exposures, which cause mutations, deplete vitamin D3 in the skin.

LIFE STYLE including smoking
Life style – outdoor/indoor life, smoking etc can influence the risk to melanoma. Smokers have lower plasma antioxidant levels than non-smokers and this leads to decreased protective efficacy of the antioxidant defense system.

CANCER SUSCEPTIBILITY
FAMILY HISTORY (GENOTYPE)
Approximately 10% of melanoma is inherited (Familial). About 40 percent of familial melanoma is associated with chromosome 9p. There are geographical variations in the melanoma susceptibility genes CDKN2A and CDK4.

DNA POLYMORPHISMS/ SOMATIC MUTATIONS
The oncogenic mutations in the B-RAF and N-RAS genes constitute the initiating somatic events followed by loss of a major check point gene mainly CDKN2A or in some cases p53 or PTEN, which is connected with high risk of melanoma. Some of the genetic variants in the DNA repair gene XRCC1 have also been associated with melanoma.

DNA REPAIR CAPACITY
There are substantial individual differences in DNA repair capacity depending on nutritional and health status of the individuals or on polymorphisms in repair genes.

ANTIOXIDANT CAPACITY
Most melanoma cases are caused by free radicals induced indirect DNA damage, therefore it is important to efficiently scavenge or neutralize the reactive oxygen species.

MECHANISMS OF ACTION
GENOME DAMAGE
UVB can directly damage DNA causing apoptosis of keratinocytes by forming the sunburn cells. UVA causes indirect (oxidative) DNA damage through reactive oxygen radicals and is responsible for 92% of melanoma cases.

BIOLOGICAL ACTIVITY
UV light and ionising radiation, can induce DNA damage. Cascade of genetic and epigenetic cganges can interfere with biological processes in cells and thus influence cell cycle and progression of cells.

Questions

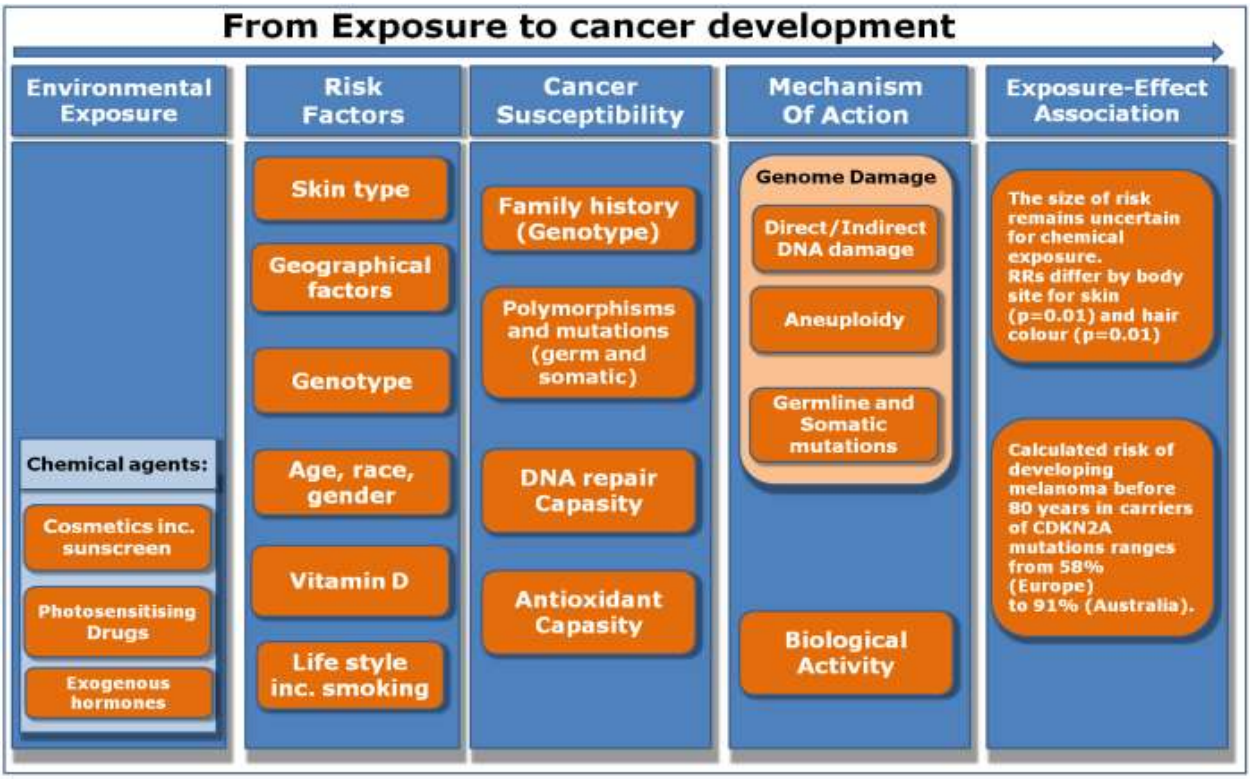
What is your level of confidence in scientists' ability to predict the impact of environmental exposure to UV and radiation on melanoma cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of individual susceptibility to UV on melanoma cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of a synergistic effect between UV and other exposure on melanoma cancer risk?

What is your level of confidence in scientists' ability to predict the impact of exposure to UV with the current knowledge of its mechanism of action on melanoma development?

MELANOMA – CHEMICAL AGENTS



RISK FACTORS

SKIN TYPE

Malignant melanoma mainly afflicts people with white skin (Caucasian population). Risk of melanoma depends on skin type.

GEOGRAPHICAL FACTORS

Sun exposure plays a primary and supporting role in most melanoma tumors. Sunscreens are used more frequently in regions with higher UV radiation.

GENOTYPE

Approximately 10% of melanoma is inherited (Familial). Mutations are found in the genes CDKN2A and CDK4.

RACE, GENDER AND AGE

Malignant melanoma mainly afflicts Caucasian population. Among cases aged 15-30 years, females have a higher risk, after age 30, incidence is higher among males.

VITAMIN D

Indoor solar UVA exposures, which cause mutations, depletes vitamin D3 in the skin.

LIFE STYLE INC. SMOKING

Life style – outdoor/indoor life, smoking etc can influence the risk to melanoma. Smokers have lower plasma antioxidant levels than non-smokers and this leads to decreased protective efficacy of the antioxidant defense system. Although sunscreens prevent sunburn, there is still missing epidemiological or laboratory evidence of protective or risk effect to melanoma.

CANCER SUSCEPTIBILITY

FAMILY HISTORY (GENOTYPE)

Approximately 10% of melanoma is inherited (Familial). About 40 percent of familial melanoma is associated with chromosome 9p. There are geographical variations in the melanoma susceptibility genes CDKN2A and CDK4.

DNA POLYMORPHISMS/ SOMATIC MUTATIONS

The oncogenic mutations in the B-RAF and N-RAS genes constitute the initiating somatic events followed by loss of a major check point gene mainly CDKN2A or in some cases p53 or PTEN, which is connected with high risk of melanoma. Some of the genetic variants in the DNA repair gene XRCC1 have also been associated with melanoma.

DNA REPAIR CAPACITY

There are substantial individual differences in DNA repair capacity depending on nutritional and health status of the individuals or on polymorphisms in repair genes.

ANTIOXIDANT CAPACITY

Most melanoma cases are caused by free radicals induced indirect DNA damage, therefore it is important to efficiently scavenge or neutralize the reactive oxygen species.

MECHANISMS OF ACTION

GENOME DAMAGE

Chemical exposure can damage DNA or directly and indirectly induce genomic changes.

BIOLOGICAL ACTIVITY

Chemical exposure can induce directly and indirectly DNA damage, oxidative damage or influence gene expression. Cascade of genetic and epigenetic cganges can interfere with biological processes in cells and thus influence cell cycle and progression of cells.

Questions

What is your level of confidence in scientists' ability to predict the impact of environmental exposure to cosmetics including sunscreen on melanoma cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of individual susceptibility to cosmetics including sunscreen on melanoma cancer risk?

What is your level of confidence in scientists' ability to predict the magnitude of the effect of a synergistic effect between cosmetics incl. sunscreen and other exposure on melanoma cancer risk?

What is your level of confidence in scientists' ability to predict the impact of exposure to cosmetics incl. sunscreen with the current knowledge of its mechanism of action on melanoma development?

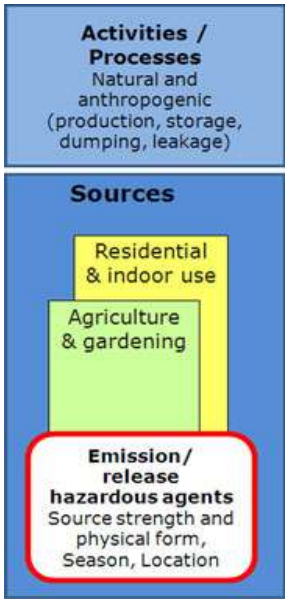
TOPIC 3: NEURODEVELOPMENTAL DISORDERS

CHLORPYRIFOS: PART A - EVALUATION OF INDIVIDUAL CAUSAL ELEMENTS

Where questions ask for your confidence level, please use these guidelines:

Very high confidence. At least a 9 out of 10 chance of being correct.	High confidence. At least an 8 out of 10 chance of being correct.	Medium confidence. At least a 5 out of 10 chance of being correct.	Low confidence. At least a 2 out of 10 chance of being correct.	Very low confidence. Less than a 2 out of 10 chance of being correct.

It is important that you consider each question independently from the others. For example, when you answer a question on routes of exposure, do not take into consideration your confidence in our ability to predict levels of exposure.



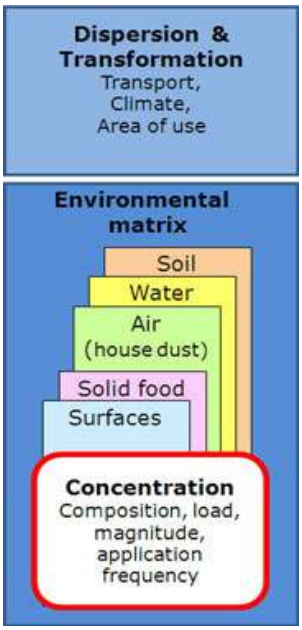
CPF Sources

1.What is your level of confidence in available data on the production volumes of CPF?*

2. What is your level of confidence in the ability to predict the magnitude of CPF release during production and use?*

3. What is your level of confidence in the available knowledge of different applications of CPF?

Do you have any comments on sources?



CPF Environmental

4. What is your level of confidence in the ability to predict the concentration of CPF in:

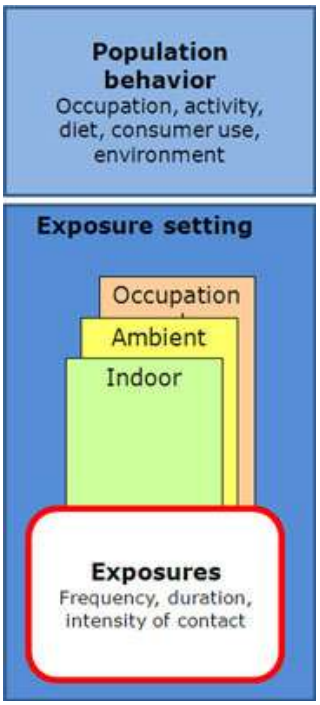
a) Soil: b)Water:

c) Air: d) Food:

e) Surfaces:

Do you have any comments on this section?

CPF Exposure



5. What is your level of confidence in scientists' ability to predict the levels of CPF from different routes of exposures:

a) Oral exposure: b) Inhalational exposure:

c) Dermal exposure:

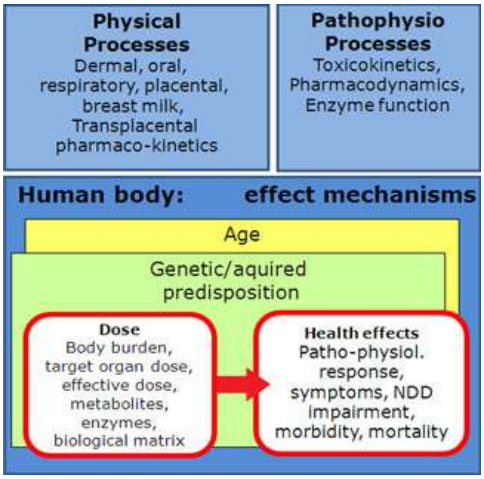
6. What is your level of confidence in scientists' ability to predict the levels of exposure to CPF in:
a) General populations b) Occupational exposed groups:

7. What is your level of confidence in scientists' ability to predict the main sources of exposure for:

a) The general population: b)Occupational exposed groups:

Comments about exposures:

CPF Human



Toxicokinetics

8. What is your level of confidence in scientists' ability to identify appropriate biomarkers for CPF exposure?*

9. What is your level of confidence in scientists' ability to predict differences in toxicokinetics among sensitive groups (age, sex, etc.)?

Toxicology/Health Effects

10. What is your level of confidence in scientists' ability to predict that CPF has the potential to cause detrimental health effects?*

11. What is your level of confidence in scientists' ability to predict sex-specific health effects in experimental animals?*

12. What is your level of confidence in scientists' ability to predict neurodevelopmental disorders in humans due to prenatal exposure?*

13. What is your level of confidence in scientists' knowledge of the mechanism(s) of action of CPF and their metabolites?*

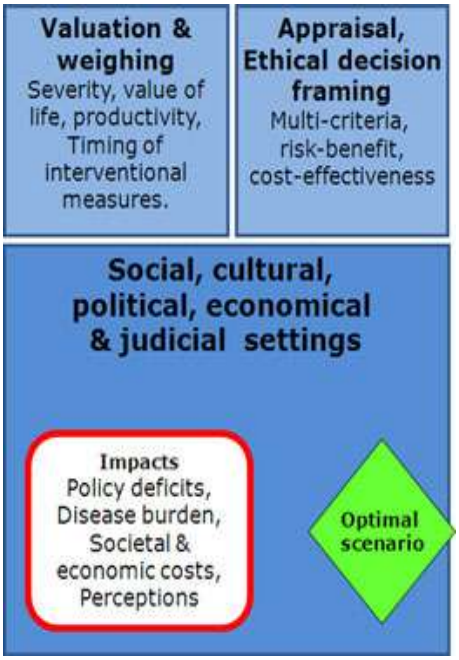
14. What is your level of confidence in the validity of the claim that CPF and its metabolites exert adverse effects on:

a) Foetal growth? *b)Somatic growth of exposed children?*

c) Central nervous system? *d)Behavioural end points?*

Do you have any comments on physical processes and effect mechanisms?

CPF Social



15. What is your overall level of confidence in the ability to predict harmful effects of CPF in the environment and on human health?

What is your level of confidence in the ability to predict the effects of CPF on neurodevelopment?*

16. Should CPFs be banned from home use due to any factors

Yes, and there is sufficient evidence
Yes, but more evidence is needed
Neither Yes nor No
No, but more evidence is needed
No, and there is sufficient evidence

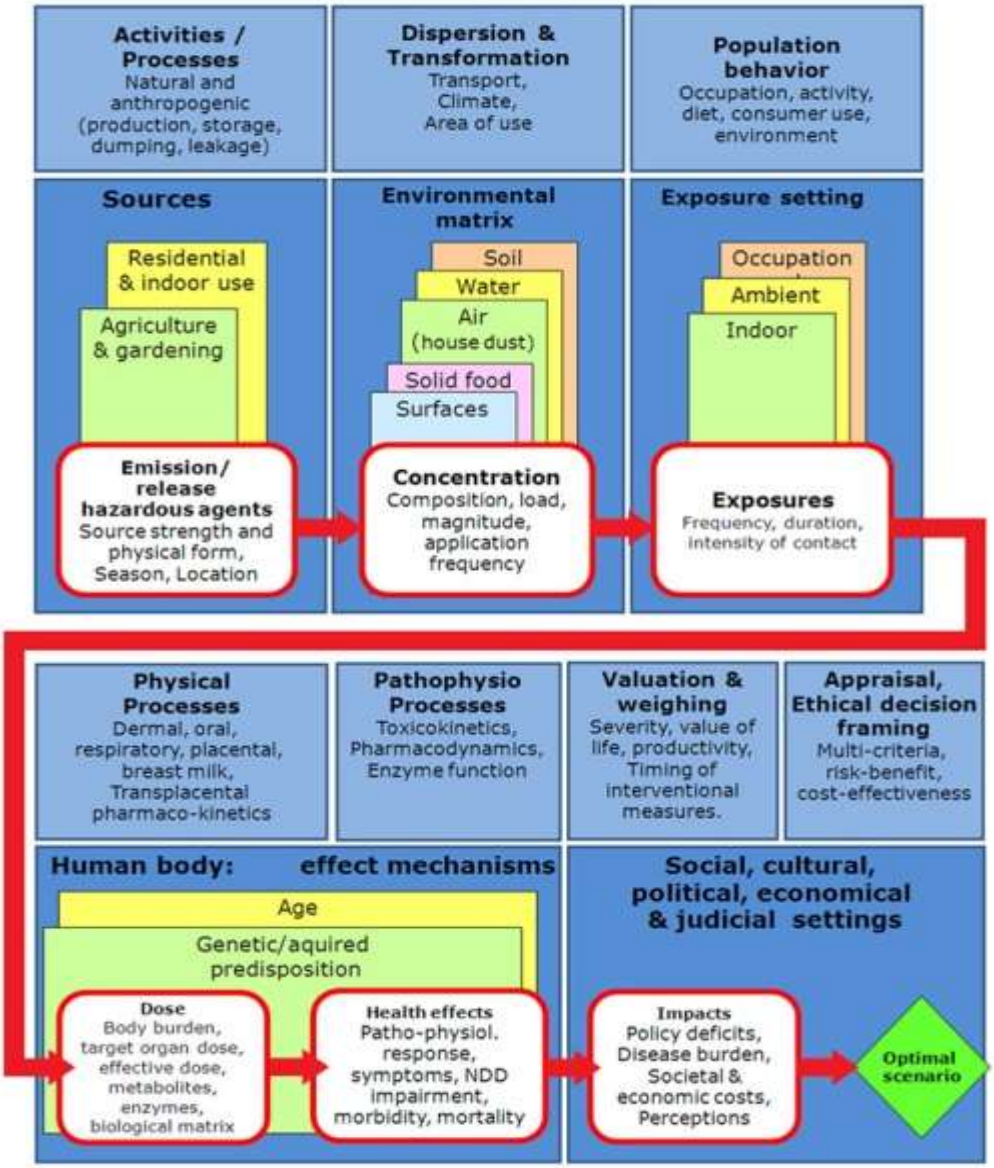
17. Should CPFs be banned for home use due specifically to neurodevelopmental effects?*

Yes, and there is sufficient evidence
Yes, but more evidence is needed
Neither Yes nor No
No, but more evidence is needed
No, and there is sufficient evidence

Do you feel there are other regulatory interventions justified by our current level of knowledge?

Do you have any comments for this page?

PART B - EVALUATION OF STRUCTURE AND COMPLETENESS OF THE CAUSAL DIAGRAM



The complete diagram is designed to illustrate the cause/effect relationship between production and usage of CPF and health effects. For a summary explanation of the scientific basis of the diagram, please see Annex 1. Now that you have considered the different causal relationships on their own, please comment on the comprehensiveness and structure of the diagram as a whole.

18. Does the diagram take into account all of the important parameters when evaluating the risks related to production, use and discharge of Chlorpyrifos? * YES/NO

If the previous answer was No, Please explain:

19. Are the different causal relationships adequately structured? * YES/NO

If the previous answer was No, Please explain:

20. Are there any unnecessary parameters shown in the diagram that could be deleted? * YES/NO

If the previous answer was Yes, please explain:

SUMMARY EXPLANATION OF THE CAUSAL DIAGRAM.

Sources

Organophosphate (OP) compounds are used worldwide in agriculture and gardening to control insect pests. They also have residential and indoor applications for pest control especially for cockroaches and termites (Van den Hazel & Zuurbier 2005, Gurunathan et al 1998, Aprea et al 2000, Morgan et al 2005, Becker et al 2006, Whyatt & Barr 2001). OPs act by inhibiting acetylcholinesterase, thus affecting nerve function in insects, humans and other animals. Most of the animal and human studies published between 2000 and 2007 refer to the OP chlorpyrifos (CPF).

OPs are used frequently in Europe for pest control due to their low price and broad spectrum of activity. In 2003 they accounted for over 59% (4645 tonnes) of insecticide sales in the EU, with CPF the top selling insecticide (15.6%, 1226 tonnes) (Eurostat 2007). CPF was also one of the most widely used OPs in the US for pest control (Gurunathan et al 1998), but the US Environmental Protection Agency (EPA) imposed a ban on the sale of CPF for residential use in December 2001 (US EPA 2000).

Activities involved in the production, storage, transport and use of CPF may play a role in release as it is transferred from the production site to the final user. Unintentional release through dumping or leakage can lead to unexpected exposure. The uptake of CPF into the environment depends on factors such as the strength at the source and the physical form (dry solid, liquid, etc.). The extent of use will also depend on the time and location. For example, agricultural and gardening use will be influenced by the seasonal growth of crops and plants, whereas residential use is less likely to be specifically influenced by seasons apart from climate effects on pest infestation. There may still be seasonal influence on child exposure (Becker et al 2006)

Environmental matrix

Dispersion and transformation of CPF from the sources affects uptake into the environment and may be influenced by transport, climate and the characteristics of the area where they are being applied. The use of CPF for agricultural and gardening purposes will lead to accumulation in soil, water and on food such as vegetables and fruit as well as atmospheric dispersal (van den Hazel & Zuurbier 2005, Aprea et al 2005, Gurunathan et al 1998, Morgan et al 2005, Becker et al 2006).

However, residential use is considered to be the main source for the majority of the population, alongside contaminated food consumption (Becker et al 2006). This can lead to accumulation in indoor air, including house dust, and on surfaces including toys (Gurunathan et al 1998, Morgan et al 2005).

Incorporation of CPF into each environmental matrix will vary according to concentration and is influenced by composition (parent compound/environmental metabolite), how the load is spread (concentrated or dispersed), and the magnitude of the load and the frequency of application.

Exposure setting

Population behaviour influences interaction between the environment/exposure setting and the extent of exposure. For CPF, there are three key exposure settings: occupational, ambient and indoor.

Occupation puts farming and greenhouse workers at risk from sources used in agriculture and gardening. Similarly, manufacturing workers are also at risk, especially if there is an inadvertent leak.

The general public, especially children, are mainly at risk from ambient and indoor residential exposure. Several physical processes are possible.

Oral exposure can arise particularly from fruit and vegetables consumed as part of the normal diet, but also water, milk and derived products (Morgan et al 2005, Aprea et al 2000). Indirect exposure occurs within the ambient and indoor settings (Morgan et al 2005, Gurunathan et al 1998, Aprea et al 2000, Becker et al 2006). Contact with soil and oral non-dietary exposure are important exposure routes for younger children due to their behaviour patterns with respect to play at floor level and on/with other surfaces and toys. Inhalation of indoor air is another route with house dust a critical component. Dermal exposure is also possible.

Exposure during pregnancy is an area of concern given the high percentage of women using pest control during pregnancy and the vulnerability of the fetus during development. Fetal exposure occurs through transplacental transfer with the placenta failing to act as a barrier to lipophilic OPs (Whyatt & Barr 2001). There is limited data concerning the presence of OP in human breast milk (Sanghi et al 2003), possibly due to partitioning into the water fraction of breast milk. This area requires further investigation as it may present an additional exposure route during the postnatal period (Rauh et al 2006).

The extent of exposure will be affected by the frequency, duration and intensity of contact which can all vary. There may also be transfer between settings. For example, a parent who is an agricultural worker may transfer residue to their offspring within the home.

Toxicokinetics

The dose of pesticides in organs and tissues is determined by the pharmacokinetics of CPF: physical absorption, distribution, metabolisms and excretion processes following uptake. An important element in assessing exposure is the biological matrix used for sampling. Levels in humans are determined through biomarkers which may be subject to interpretation.

For CPF, the most commonly used biomarkers are found in blood and urine. In blood, exposure is determined by measurement of plasma butyrcholinesterase (BuChe) activity and erythrocyte acetylcholinetserase (AChE) activity (Albers et al 2007). Urine measurements detect excretion of metabolites. This is more widely used for young children compared with taking blood samples. CPF is activated in the liver to CPF oxon by cytochrome P450-dependent desulfuration (Needham 2005).

Measurements of CPF or CPF oxon are the most specific marker for exposure (Barr & Angerer 2006). However, organophosphates are rapidly metabolized in the body and almost entirely excreted in the urine (Aprea et al 2000). Some may be stored in adipose tissue (Barr & Angerer 2006), meaning that parent compound levels in blood are very low compared with metabolites.

The specific CPF metabolite 3-5-6 trichloro-2-pyridinol (TCPy) can be detected in urine (Berkowitz et al 2004, Eskenazi et al 2004) as can the non-specific OP dialkyl phosphate (DAP) metabolites formed from nearly all OP insecticides (Becker et al 2006). For CPF, these DAP metabolites are diethyphosphate (DEP) and diethylthiophosphate (DETP). However, about 75% of OP pesticides are also biotransformed to DETP, DEP or other DAPs measured in the same way and they cannot be distinguished from environmental degradates (Needham 2005). Careful interpretation is needed when measuring DAPs as they cannot necessarily be correlated with specific OP insecticides and the metabolites themselves may be ingested (Becker et al 2006).

Route of exposure will affect the absorption and hence body burden and target organ dose. A case study of CPF and malathion biomonitoring demonstrated that about 70-93% of the oral dose of CPF could be recovered in the urine but only 1-3% of the dermal dose was (Barr & Angerer 2006). Pharmacokinetics also influence organ dose and effective dose through distribution, metabolite production and enzyme function. OP pesticides can be converted to the oxon form which interacts with available cholinesterase. However, the oxon form can also be enzymatically or spontaneously hydrolysed to form a DAP metabolite and an organic metabolite. Unconverted OP can also be hydrolysed to the organic group metabolite and DAP metabolites (Barr & Angerer 2006). These metabolites or their conjugates are excreted in urine.

Health effects

Age and genetic/acquired predisposition may determine health effects from the CPF exposure dose. CPF toxicitiy is due to the inhibition of acetylcholinesterase by the CPF oxon, preventing efficient degradation of acetylcholine and leading to accumulation of transmitter molecules in the nerve synapse. Elevated synaptic acetylcholine levels result in persistent receptor stimulation and the alteration of signalling pathways with functional changes at tissue/organism level (Pope et al 2005).

Health effects following occupational exposure in adults include impaired memory and concentration, disorientation, severe depression, irritability, confusion, headache, speech difficulties, delayed reaction times, nightmares, sleepwalking, insomnia and flu-like symptoms (Barr & Angerer 2006).

Animal and *in vitro* studies suggest that CPF can act by other mechanisms and have clearly shown that CPF exposure at doses below the threshold for systemic toxicity and inhibition of brain cholinesterase exerts disruptive effects on neural cell development, with respect to DNA synthesis, gene transcription, cell differentiation, and synaptogenesis (Crumpton et al 2000).

Several rat studies have indicated that CPF targets neurotransmitter systems further to the cholinergic one, as the monoamines, norepinephrine, dopamine, and serotonin (Aldridge et al., 2004). In addition, glial cells are more sensitive to CPF than neurons and may be preferentially targeted (Colborn 2006). Interference with brain maturation is associated with behavioral disturbances in exposed rodents, including hyperactivity, learning impairment and alterations in the social and emotional domain (Aldridge et al 2005, Carr et al 2001, Dam et al 2000, Levin et al 2001, Ricceri et al 2003 & 2006). This suggests vulnerability during fetal and childhood periods (Berkowitz et al 2004).

CPF is considerd moderately toxic and is an EPA class II toxicant i.e. oral dose LD50 is 50-500mg/kg (Barr & Angerer 2006).

Juvenile and prenatal susceptibility

Animal studies have demonstrated that juveniles are more susceptible to OP toxicity than adults (Furlong et al 2005). Animal and *in vitro* studies show low-dose OP exposure in pre- or early post-natal period produces neurochemical and neurobehavioural changes (Berkowitz et al 2004). This is attributed to incomplete metabolic competence during development (Kousba et al 2007) and the susceptibility of the rapidly developing nervous system.

Paraoxonase 1/arylesterase (PON1) is a key OP detoxifying enzyme. Increased sensitivity to OP toxicity in newborns may be due to reduced PON1 levels, which are 3- to 4-fold lower than in adults. There is considerable PON1 polymorphism and this genetic variability will affect sensitivity alongside a 13-fold variation in adult levels (Furlong et al 2005 & 2006).

Additional noncholinergic mechanisms - such as oxidative stress - may damage the developing brain with exposures occurring below the systemic effects threshold. Thus nonsymptomatic exposure for pregnant women, infants and children and could be linked with increased risk for development of metabolic diseases such as diabetes (Slotkin et al 2005).

Neurodevelopmental toxicity is of concern in prenatal and early postnatal periods. Prenatal residential exposure to CPF of inner city children assessed at age 3 years was linked with impaired motor skills and impaired mental development. Highly exposed children more likely to exhibit clinical symptoms of attention problems, ADHD and pervasive developmental disorders (Rauh et al 2006).

In utero exposure of children born in an area of major agricultural production was associated with impaired reflex functioning, particularly in those assessed after 3 days postnatal (Young et al 2005). Organophosphate poisoning in children under the age of 3 was linked with impaired verbal learning and motor inhibition tasks, with higher impulsivity in OP intoxicated children (Kofman et al 2006).

In mother-infant pairs exposed to indoor residential pesticide exposure, a positive trend was found between maternal PON1 activity and head circumference in offspring where maternal CPF metabolite (TCPy) were above the limit of detection (Berkowitz et al 2004). Eskenazi et al (2004) found an association between increased levels of dimethyl phosphate metabolites (coming from malathion) in the urine in later pregnancy and a reduced gestational duration.

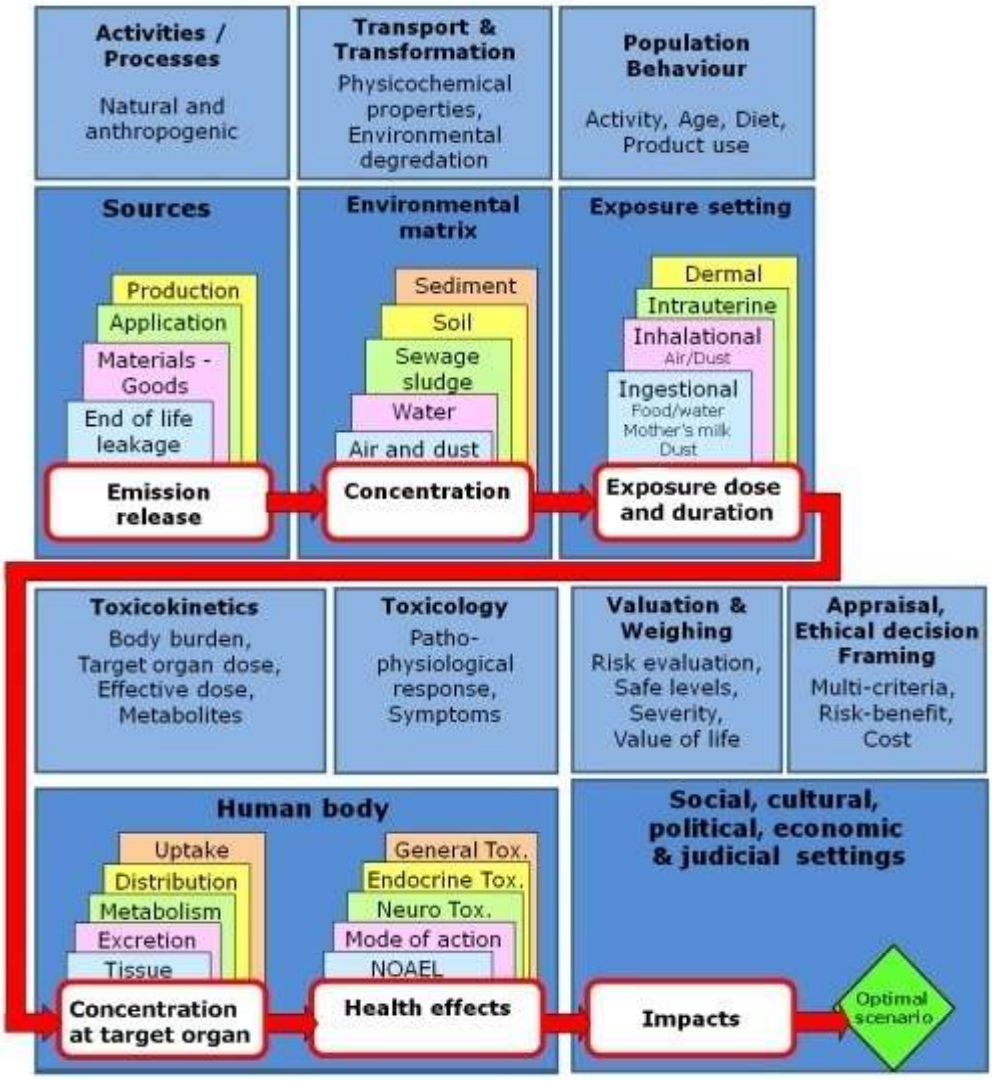
Also in that study a reduced length of gestation was found in relation with the cholinesterase levels (ChE) in umbilical cord whole blood. Maternal dialkyl phosphate metabolite levels and ChE levels in later pregnancy were not correlated. Unexpectedly, there was a positive effect of the dialkyl phosphate metabolite levels on head circumference after correction for creatinine levels. In contrast, Whyatt et al (2004) found a significant inverse correlation between cord blood plasma CPF levels and birth weight and length for children born before the 2001 ban. Later follow-up of this group revealed neurodevelopmental abnormalities at the age of 3 in relation to prenatal exposure to CPF parent compound as could be expected considering the intra-uterine growth retardation. (Rauh et al 2006)

Further studies would benefit from careful consideration of the foetal toxicokinetics and exposure time frame.

TOPIC 4: ENDOCRINE DISRUPTORS

BFR HBCD: PART A - EVALUATION OF THE STRUCTURE AND COMPLETENESS OF THE DIAGRAM

The diagram shown in the figure below illustrates the cause-effect relationship between production and emission of HBCD and health effects. For a summary explanation of the scientific basis of the diagram, please see Annex 1.



Does the diagram take into account all of the important parameters when evaluating the risks related to production, use and discharge of HBCD?* YES/NO

If you said no to the previous question, Please explain:

Are the different causal relationships adequately structured?* YES/NO

If you said no to the previous question, Please explain:

Are there any unnecessary parameters shown in the diagram that could be deleted?* YES/NO

If you said yes to the previous question, Please explain:

PART B - EVALUATION OF INDIVIDUAL CAUSAL ELEMENTS

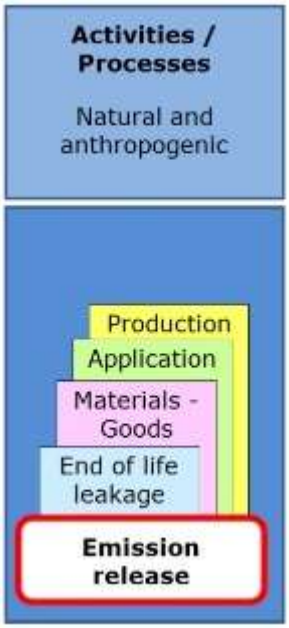
In the questions that follow you will be asked to express your confidence in scientists' ability to predict the concentrations, exposure and effects of HBCD. Insert a check mark where you feel it is appropriate.

It is important that you consider each question independently of the others. For example, when you answer a question on excretion, do not take into consideration your confidence in the scientists' ability to predict absorption.

Where questions ask for your confidence level, please use these guidelines:

Very high confidence. At least a 9 out of 10 chance of being correct.	High confidence. At least an 8 out of 10 chance of being correct.	Medium confidence. At least a 5 out of 10 chance of being correct.	Low confidence. At least a 2 out of 10 chance of being correct.	Very low confidence. Less than a 2 out of 10 chance of being correct.

Sources



1. **Regarding HBCD, what is your level of confidence in the quality of the current scientific data on:**

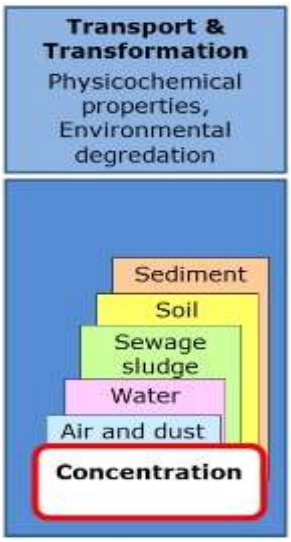
   a) Production volumes* b) Application volumes*

2. **Regarding the use of HBCD in products, what is your level of confidence in the scientists' ability to:**

   a) Identify and quantify all different applications*

   b) Predict the magnitude of emission/release/leakage during production, use and recycling*

Environmental matrix



3. **Regarding HBCD, what is your level of confidence in the scientists' ability to predict:**

   a) Environmental transformation, such as conversion of diastereomers and biological half-lives?*

   b) The magnitude of long-range transport?*

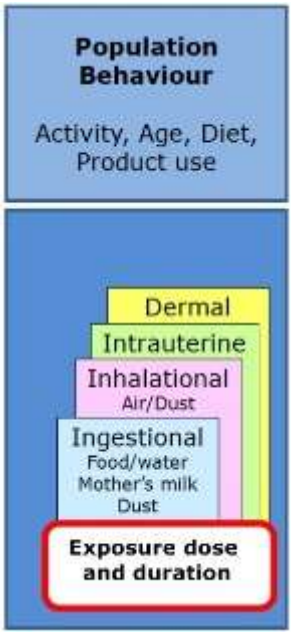
4. **What is your level of confidence in the scientists' ability to predict the <u>concentration</u> of HBCD in:**

   a) Sediments?* **b)** Sewage sludge?* **c)** Soil?*

   d) Water?* **e)** Dust?* f) Indoor Air?*

   g) Outdoor Air?*

Exposure



5. **What is your level of confidence in the scientists' ability to predict the <u>level of exposure</u> to HBCD in:**

   a) The general population?* b) Occupationally exposed?*

   c) Infants and children?*

6. **What is your level of confidence in the scientists' ability to predict <u>the main sources of exposure</u> to HBCD in:**

   a) The general population?* b) Occupationally exposed?*

   c) Infants and children?*

7. **What is your level of confidence in the scientists' ability to predict the exposure of <u>the general population</u> to HBCD via the following routes:**

   a) Direct contact/dermal?* b) Inhalation?* c) Ingestion?*

8. **What is your level of confidence in the scientists' ability to predict the exposure of <u>occupationally exposed</u> groups to HBCD via the following routes:**

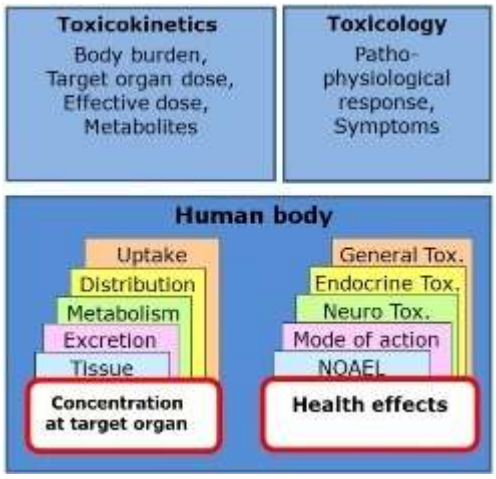
   a) Direct contact/dermal?* b) Inhalation?* c) Ingestion?*

9. **What is your level of confidence in the scientists' ability to predict the exposure of <u>infants and children</u> to HBCD via the following routes:**

   a) Direct contact/dermal?* b) Inhalation?* c) Intrauterine?*

   d) Via food? e) Via breast milk?

Toxicokinetics



10. **What is your level of confidence in the scientists' ability to predict to what extent HBCD is:**

    a) Absorbed/taken up?

    b) Metabolised to other diastereomers after absorption?

    c) Metabolised to hydroxymetabolites after absorption?*

    d) Metabolised to debrominated metabolites after absorption?*

    e) Accumulating in the body?*

    f) Excreted via bile and faeces?*

    g) Excreted via urine?

11. **Regarding HBCD, what is your level of confidence in the scientists' ability to predict**

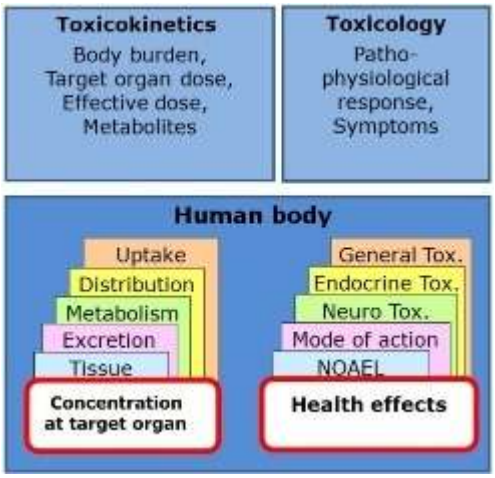
    a) The distribution to different tissues?*

    b) The final concentration of <u>the parent compound</u> in the target tissues, taking factors such as absorption, distribution, metabolism and excretion into account?*

    c) The final concentration of <u>metabolites</u> in the target tissues, taking factors such as absorption, distribution, metabolism and excretion into account?*

    d) The biological half-life?*

Toxicology



a) **Based on <u>human epidemiological studies</u>, what is your level of confidence in the scientists' ability to predict adverse effects of HBCD in**

    a) Males?* b) Females?*

12. **Based on experimental animal studies, what is your level of confidence in the scientists' ability to predict adverse effects of HBCD on <u>general health</u> in**

    a) Males?* b) Females?*

13. **Based on experimental animal studies, what is your level of confidence in the scientists' ability to predict adverse effects of HBCD on <u>nervous system</u> in**

    a) Males exposed as adults?* b) Females exposed as adults?*

    c) Males exposed during foetal or neonatal life?*

    d) Females exposed during foetal or neonatal life?*

14. Based on experimental animal studies, what is your level of confidence in the scientists' ability to predict adverse effects of HBCD on <u>thyroid function</u> in

a) Males exposed as adults?* b) Females exposed as adults?*

c) Males exposed during foetal or neonatal life?*

d) Females exposed during foetal or neonatal life?*

15. Based on experimental animal studies, what is your level of confidence in the scientists' ability to predict adverse effects of HBCD on <u>reproductive function</u> in

a) Males exposed as adults?* b) Females exposed as adults?*

c) Males exposed during foetal or neonatal life?*

d) Females exposed during foetal or neonatal life?*

16. Based on experimental studies, what is your level of confidence in the scientists' knowledge of the mechanisms of action of

a) HBCD?* b) α – HBCD? c) β – HBCD? d) γ – HBCD?

e) Other metabolites of HBCD?*

17. What is your level of confidence in the scientists' ability to predict the NOAEL of HBCD?*

18. Final comment

Finally, do you think that any relevant questions were left out or that any questions were superfluous?
Please describe:

BACKGROUND INFORMATION ABOUT HEXABROMOCYCLODODECANE (HBCD)

This document is built up according to the cause-effect chain as defined by the HENVINET. It is intended as support for the expert evaluators when answering the questionnaire and will not be submitted to a scientific journal.

The literature reviewed was sampled after the following criteria:

PubMed searches: Review articles published in 2007 and 2008

Google searches: Reports from 2007 and 2008

PubMed searches: Research papers from 2008 and 2009 where the latest news in the field were needed, such as for toxicological effects.

The document is mainly based on Law et al. (2008) and the HBCD EEC Risk Assessment (2007).

Sources

Production

Hexabromocyclododecane (HBCD) stands third in production volume (8.2%) of brominated flame retardants (BFRs) after tetrabromobisphenol A (TBBPA) (58.7%) and the decabromodiphenyl ether mixture (DecaDBE) (27.5%) (Zegers 2005).

Total global production of HBCD in 2001 was 16,700 tons (BSEF 2007).

Of the global production in 2001 about 60% were consumed in Europe and 20% in North America and 20% in Asia (Janak 2005 and Marvin 2006).

HBCD is produced in USA, Europe and Asia. The sole production site today in Europe is in the Netherlands, with an annual production volume of 6000 tons in 2005 (HBCD Risk Assessment, EEC, April 2007).

Commercial formulations of HBCD are 75-89% γ-HBCD, 10-13% α-HBCD and 1-12% β-HBCD.

Application

HBCD is used as a flame retardant additive first of all in polystyrene insulation foam, but in addition it is used in upholstery textiles and video or audio equipment castings. Finally, use has been reported in crystal and high –impact polystyrene, SAN (Styrene-AcryloNitrile) resins, adhesives, and coatings (EPA 2008).

Materials – Goods (HBCD Risk Assessment, EEC, April 2007).

Expanded polystyrene (EPS) (major product)-Used for Insulation in: Construction, Insulation boards, Packaging material (minor, not food).

Extruded polystyrene (XPS) (major product)-Used for Insulation in: Construction & Insulation boards.

High impact polystyrene (HIPS) (minor product)-Electrical and electronic equipment in: VCRs, electric castings, distribution boxes, cassette castings.

Polymer dispersion on cotton/synthetic blends-used as a textile coating agent: Upholstery fabric, bed mattress ticking, upholstered furniture, seatings, draperies, wall coverings, interior textiles, automobile indoor textiles.

End of life leakage

HBCD is not covalently bonded to the material leading to the risk of migration out of the product during use or disposal (Tomy 2005).

In a study of amount and presence of BFRs originating from electrical, electronic equipment and construction materials in a Swiss recycling plant, HBCD was measured to be 17 mg/kg of bulk waste (Morf 2007).

A large and variable percentage of HBCDs in the atmosphere (69.1-97.3 %) existed in the particle phase, and suggest that long-range transport is possible in some environmental conditions (Yu 2008).

Environmental Matrix

HBCD are ubiquitous contaminants in the environment, wildlife and humans due to widespread use, low volatility and low water solubility (Covaci 2006).

Biotransformation and half-lives

Biologically mediated transformation and anoxic conditions accelerate the rate of loss of HBCD. The biotransformation half-lives were 63 and 6.9 days in aerobic and anaerobic soils, and the biotransformation half-lives ranged from 11 to 32 days and 1.1 to 1.5 days in aerobic and anaerobic river system conditions (Davis 2005).

Microorganisms naturally occurring in aquatic sediments and anaerobic digester sludge debrominate HBCD via dihaloelimination. Metabolites identified were tetrabromocyclododecane, dibromocyclododecadiene, cyclododecatriene (Davis 2006).

Degradation of HBCD (a technical mixture) under anaerobic conditions in sewage sludge in a laboratory system gave a half-life of 0.66 days. Half-life of α-HBCD was double of β-HBCD and γ-HBCD (Gerecke 2006).

Sediment

Total HBCD concentrations of North Sea surface sediments were from <0.2 to 6.9 µg/kg dry weight (n=10) (Klamer 2005).

HBCD concentrations from the German Bight were from 0.03 to 6.5 µg/kg dry weight (n=12) (Lepom 2007).

HBCD was only detected in the depth interval from 1 to 2 cm, α -HBCD = 0.43 µg/kg dry weight, γ -HBCD = 3.9 µg/kg dry weight, β -HBCD was not detected (n=4) (Evenset 2007). There has been a more than 5-fold increase in Sum-BDE concentrations in the lake sediments over the last 50 years.

Three sediment cores and six surface sediment samples from Tokyo Bay were analysed (Minh 2007). Sum-HBCD was ranging from 0.06 to 2.3 µg/kg dry weight, implying widespread contamination (n=3).

Levels were higher near to the highly populated industrial area of the bay indicating industrial and human activities as sources. HBCD first appeared in sediment cores in the mid-1970s and increased since then. The annual surface flux to sediments currently is: Sum-HBCD=0.6-2.4 ng/cm2/year.

Swiss lake sediments showed that the concentration of HBCD was continuously increasing to reach 2.5 ng/g dry weight in 2001 (Kohler 2008).

Soil

Very little data is available on HBCD concentrations in soil.

Concentration in soil from urban areas in China ranged from 1.7 to 5.6 ng/g dry weight (n=3) (Yu, Peng et al 2008).

Soil samples from near-point sources in Sweden and Belgium/Germany ranged from 111 to 23,200 ng/g dry weight (Covaci 2006).

Sewage sludge

HBCD was determined in sewage sludge from eight locations in the Czech Republic, and in sediments downstream of the sewage plant. HBCD concentration was 1-27 µg/kg dry weight (n=8) (Pulkrabova 2007).

Water

Data for BDEs in dissolved and suspended phases of water samples is usually not gathered because of their high degree of hydrophobicity, which will cause adsorption to particulate matter and deposition in sediments as potential sinks and sources (Law 2008).

Air

Outdoor air

13-15 pg/m3 Sum-HBCD (n=2) outside Japanese homes (Takigami 2007).

1.2-1.8 pg/m3 (n=4) in Guangzhou city in South China (Yu, Peng et al 2008). Mean percentages of β-HBCD, α-HBCD and γ-HBCD were 58%, 15% and 27% respectively, which differs from commercial mixtures and may be due to leaching from the high temperature treated products.

Indoor air

Sum-HBCD = 6.7 and 280 pg/kg in indoor air in Japan (n=2) (Takigami 2007).

Long-range transport

A large and variable percentage of HBCDs in the atmosphere (69.1-97.3 %) existed in the particle phase, and suggest that long-range transport is possible in some environmental conditions (Yu 2008).

Exposure

Humans can be exposed to HBCD by inhalation of vapour and airborne dust, through ingestion and by dermal contact. Babies can be exposed during pregnancy and breast-feeding. Workers and consumers are mainly exposed through inhalation and dermal routes, exposure via the environment is mainly through the oral route Netherlands (HBCD Risk Assessment, EEC, April 2007).

Intrauterine

HBCD can be transferred to infants through cord blood.

A Dutch study of mothers (n=90) and infants (n=90) showed that HBCD was detected in almost all samples (Weiss 2004). Cord blood showed a mean of 2.4 ng/g lipid weight, a median of 0.32 ng/g lipid weight and a range of 0.16-4.2 ng/g lipid weight. Mothers' serum showed a mean of 1.1 ng/g lipid weight, a median of 0.72 ng/g lipid weight and a range of 0.16-6.9 ng/g lipid weight.

Mother's milk, human

HBCD is transferred to infants through mother's milk, and increased concentrations in the milk have been measured over time.

One of the highest levels of HBCD in mother's milk was measured in Mexico with an average of 2.1 ng/g lipid (range of 0.8-5.4 ng/g lipid and n=7) (Lopez 2004).

One of the lowest average levels measured were in Sweden in 1980 (average 0.084 ng/g lipid and n=116). The levels in the Swedish study were shown to increase until 2002 (average of 0.75 ng/g lipid and n=20), where after the levels decreased (average of 0.39 ng/g lipid and n= 20, measured in 2004) (Fangstrom 2005, Fangstrom 2006).

Food/Water

A typical exposure level of 3 ng HBCD/kg/day, a maximum level of 22 ng HBCD/kg/day, and a level of 20 ng HBCD/kg/day is considered in the risk characterization (HBCD, Risk Assessment, EEC, April 2007).

A regional average concentration of HBCD in fresh water fish based on all EU data has been estimated to be 20 µg/kg wet weight. Based on this a daily intake of HBCD from fish is approximately 33 ng HBCD/kg bwt/day.

A screening study on a limited number of different samples of food in Sweden (fish, chicken, milk and egg) and the amount of food normally consumed of these food types, resulted in a calculated estimated maximum intake of 22 ng HBCD/kg/day. The medium value was 10-fold lower (Lind 2002).

An average dietary intake of HBCD in the Dutch population was estimated to be 3 ng HBCD/kg bwt/day, from measuring the concentration of HBCD in 91 samples of food like dairy, meat, animal fat, eggs, fish and vegetable oil (De Winter-Sorkina 2003).

Dermal

Only estimated values exist for dermal exposure.

Occupational, estimated (HBCD, Risk Assessment, EEC, April 2007).

Occupational exposure: Manufacture of HBCD: 1-5 mg/cm^2/day, this is equivalent to 4200 mg/day if assuming exposure of two hands.

Occupational exposure: Industrial use of HBCD as an additive (formulation and processing in the polymer industry): 84 and 120 mg/day for XPS/EPS-production and textile coating, respectively. For granules, the exposure is thought to be 10 % of that with powder, because of less dusting, i.e., 8.4 mg/day.

*Occupational exposure: during industrial end-use of semi- and end-products containing HBCD:*A total exposure is estimated to be 84 mg HBCD/day

Consumer, estimated (HBCD, Risk Assessment, EEC, April 2007).

A consumer exposure assessment of HBCD was made on dermal exposure assuming exposure from furniture upholstery back-coated with HBCDD, estimated to be 1.3×10^{-6} mg/kg/day.

Inhalation

Occupational, estimated (HBCD, Risk Assessment, EEC, April 2007).

Occupational exposure: Manufacture of HBCD: A typical level of exposure via inhalation can be about 0.95 mg/m^3, representing 4h contact with the standard grade substance

Occupational exposure: Industrial use of HBCD as an additive (formulation and processing in the polymer industry): For HBCD charging to a process, reasonable worst-case exposure levels for fine grade and standard grade HBCD is 2-5 mg/m^3.

Occupational exposure: during industrial end-use of semi- and end-products containing HBCD: The air concentration is estimated to be 0.5 mg/m^3

Consumer, estimated (HBCD, Risk Assessment, EEC, April 2007).

Air

A consumer exposure assessment of HBCD was made. Inhalation exposure in a room caused by wear of and evaporation of HBCD from fabric upholstery treated with HBCD, is estimated to give a total air concentration of 3.9 µg/m^3 HBCD.

Indoor air exposure: Estimated to be 0.002 µg/kg bwt/day.

Mattress ticking: Estimated to be 0.01 µg/kg bwt/day.

Dust

Oral Exposure to dust: Assuming the daily amount of dust available for oral exposure would be 2.5 mg/day, the content of HBCD in the dust was 0.47 %, leading to an oral exposure to 12 µg HBCD/day. If a 10 kg child is eating all dust generated from the sofas, the daily exposure would become 1.2 µg/kg/day, the internal exposure will be 1.5 µg/kg bwt/day.

Oral Exposure to mouthing a textile: Estimated to be 3 µg/kg bwt/day.

Consumer, measured:

Very little data has been reported. Different sampling methods can give different results (e.g. passive samplers like PUF disks that only collect the particulate phase and active samplers like Hi-Vols that primarily measures the gas phase) (Abdallah 2008).

Air

Air in homes in Japan (n=2) SHBCD = 6.7 and 280 pg/kg indoor air (using Hi-Vol samplers) (Takigami 2007).

Outdoor air in Guangzhou city in South China 1.2-1.8 pg/m^3 (n=4). Mean percentages of β-HBCD, α-HBCD and γ-HBCD were 58%, 15% and 27% respectively, which differs from commercial mixtures and may be due to leaching from the high temperature treated products (Yu, Peng et al 2008).

Dust

Sum-HBCD α-, β-, γ-diastereomers in UK: house dust was on average = 6000 µg/kg (n=31), office dust was on average = 1400 µg/kg (n=6) indistinguishable from North American domestic dust. The diastereomer pattern in dust fell between commercial formulations (predominantly γ-) and human tissues (predominantly α-) (Abdallah 2008).

Dust in homes in Japan (n=2) SHBCD=240 and 13,000 µg/kg in dust (Takigami 2007).

Toxicokinetics

HBCD is lipophilic and has a bioaccumulation factor log Kow of 5.6 and is considered bioavailable and bioaccumulative (Marvin 2006).

Uptake

The studies below were used for risk characterization; the oral and inhalation absorption were set to 100 % and 2-4 % for the dermal absorption, depending on the size of the particles (Yu & Atallah 1980, Roper 2005, HBCD, Risk Assessment, EEC, April 2007).

Inhalation

No studies are available on absorption through inhalation, but it was set to be 100% (HBCD, Risk Assessment, EEC, April 2007).

Oral

Animal studies demonstrate that HBCD can be absorbed from the gastro-intestinal tract.

The estimated absorption half-life in a rat study was 2 hours from the gastrointestinal tract and peak radioactivity in blood was reached 4 hours after administration, and at 8 hours 43% of the administered dose was recovered in tissues. 93% of the dose was excreted within 3 days as transformed substance (metabolites), therefore an oral absorption close to 100% is indicated (Yu & Atallah 1980).

Based upon a study in Labradors using felodipine (a substance similar to HBCD due to its poor water solubility), the LOAEL of HBCD in a rat study was adjusted to a corrected LOAEL based on an expected 10-20 % oral absorption (Chengelis 2001).

Dermal

The total dermal absorption was estimated to be 4%, based on a human *in vitro* skin test study (Roper 2005).

Distribution

The highest concentrations of HBCD are reached in adipose tissue and muscles followed by liver, and very little is found in lung, kidney, blood, brain, and gonads (Yu & Atallah 1980). During long-term exposures, females achieved higher concentrations than males (4342 µg/g fat in females and 3101 µg/g fat in males was measured in one rat study), but HBCD is bioaccumulating in both sexes (Chengelis 2001). The α-diastereomer is much more accumulating than the others (the relative bioaccumulation factor is 99:11:1 for α-, β- and γ- HBCDD, respectively) (Zegers 2004). It takes months to reach steady-state (HBCD, Risk Assessment, EEC, April 2007).

Tissue Levels

Adipose tissue and other organs, experimental animals

In a rat study using γ-HBCD, after 8 hours the highest concentration was found in adipose tissue, and muscle followed by liver. Very little was found in lung, kidney, blood and brain. After 8 hours 43% was recovered in tissues: 20% in fat, 14% in muscle, 7 % in liver and 0.2 % in gonads. After 24 hours 0.8% was found in the liver. After 48 hours 14% was found in fat, 3% in muscle and 0.5% in the liver. At 72 hours 14% was still found in fat, but the amount in muscle was reduced to 2% and the amount in liver to 0.28% (Yu & Atallah 1980).

Mother's milk (human)

One of the highest levels of HBCD in mother's milk was measured in Mexico with an average of 2.1 ng/g lipid (range of 0.8-5.4 ng/g lipid and n=7) (Lopez 2005). One of the lowest average levels measured were in Sweden in 1980 (average 0.084 ng/g lipid and n=116). The levels in the Swedish study were shown to increase until 2002 (average of 0.75 ng/g lipid and n=20), where after the levels decreased (average of 0.39 ng/g lipid and n= 20, measured in 2004) (Fangstrom 2005, Fangstrom 2006).

Blood (human)

In a Dutch study of 90 mothers and newborns, cord blood showed a mean of 2.4 ng/g lipid weight and a range of 0.16-4.2 ng/g lipid weight (Weiss 2004). Mothers' serum showed a mean of 1.1 ng/g lipid weight and a range of 0.16-6.9 ng/g lipid weight. Similar levels were found in 5 mothers in Mexico (Lopez 2004) and in mothers in the Netherlands (Meijer 2008). Another Dutch (Weiss 2006) study showed that the blood samples contained mostly the α-HBCD diastereomer with only a few percents γ-HBCD .

Comment: The blood levels of HBCD in different studies are measured in plasma, serum or whole blood and given as ng/g lipid weight, ng/ml plasma or ng/g blood and are thus difficult to compare without taking into account the percentage of fat.

Metabolism

HBCD diastereomer ratios differ in environmental matrix and in biota from the commercial mixtures, with a shift from the more common stereoisomer γ-HBCD in the technical mixture to a prevalence of the α-HBCD stereoisomer (Covaci 2006).

In biota the cytochrome P450 system preferentially metabolises the γ- and the β-diastereomers, but not the α-diastereomer. α-HBCDD is not accumulated in tissue by stereoselective degradation, but through preferential accumulation or stereoselective uptake (Zegers 2004).

In a 90-minutes incubation of HBCD with hepatic microsomes, the β- and γ-diastereomer seemed to decrease (69% and 60% decrease, respectively), whereas no significant disappearance of α-HBCDD was observed (17% decrease) (Zegers 2004). For β-HBCD and γ-HBCDD respectively, three and two bromine-containing metabolites could be observed. Hydroxy-metabolites of both the β-diastereomer and γ-diastereomer were found.

In a rat study using γ-HBCDD, after 3 days 93% of the administered dose was excreted as metabolized HBCD (Yu & Atallah 1980).

In a rat study the mean levels of HBCD after 89 days was 3101 µg/g fat for males and 4342 µg/g fat for females (Chengelis 2001). The concentration in females were always higher than in males (15-100% more). In addition a 100-fold higher relative bioaccumulation of the α-HBCDD diastereomer than the major γ-HBCDD diastereomer.

Excretion

Elimination of HBCD and its metabolites mainly occurred via faeces, with a minor part excreted in urine. Elimination from body fat appears to be markedly slower than from other tissues, with an elimination half-life of the three diastereomers possibly being in the order of weeks to months (HBCD Risk Assessment, EEC, April 2007).

In a rat study (n = 8 females and 2 males), after 48 hours 94% in males vs 54 % in females of the administered dose was eliminated in faeces (Yu & Atallah 1980). After 72 hours 77% of the HBCD and its metabolites were found in faeces and only 16% in urine.

In a rat study (n = 4 males), 24 hours post dosing, no urinary excretion of unchanged HBCD was found (Arita, Miyazaki & Mure 1983). Faecal excretion of 29-37 % of the administered amount was found to be the average daily rate.

Toxicology

General Toxicology

Acute toxicity

The HBCD substance tested has a very low acute toxicity by oral and dermal exposure, and it has not been possible to determine a LD50 value. The minimum oral lethal dose is > 20 g/kg in rats (Wilson and Leong 1977 and Lewis and Palanker 1978), and > 40 g/kg in mice (EPA 1990 and Tobe 1984). LD_{50} of dermal exposure is > 20 g/kg in rabbits (Wilson and Leong 1977 and Lewis and Palanker 1978). The acute toxicity by inhalation has not been investigated properly, but seems to be low.

Irritation

HBCD is mildly irritating for the eye, but not enough to classify as an eye irritant according to EU criteria (Wilson and Leong 1977 and Lewis and Palanker 1978). HBCD is not irritating to skin in skin irritation studies or to the respiratory system according to clinical symptoms in acute toxicity studies by the inhalation route (Wilson and Leong 1977 and Lewis and Palanker 1978).

Corrosivity

HBCD is not corrosive to skin, based on a rabbit study (Crown 1984).

Sensitisation

Human studies show that no skin reactions were observed (McDonnell 1972). Two animal studies performed on a composite of EU-marketed HBCD (1-50%, n= 20 and 12 or 30) gave negative results (a Magnuson-Kligman and a Local Lymph Node test), and showed that this composite of HBCD can not be considered to be sensitising (Wenk 1996 and Wolhiser & Anderson 2003). However, two positive animal studies performed in Japan on HBCD of unknown origin and purity (0.005-5%, n=10), indicates that such HBCD may contain sensitising constituents (Nakamura 1994 and Momma 1993).

Endocrine Toxicology

Liver effects

The only really consistent effect from HBCD exposure is liver weight increase in female rats, and in most studies also in male rats. Hepatic enzyme induction is clearly involved and likely the cause of weight increase.

Liver weights were increased in both sexes in rat studies with doses from 0 to 940 mg/kg/day (Zeller and Kirsch 1969 & 1970, Chengelis 1997 & 2001, van der Ven 2006).

HBCD exposure in male and female rats (0-100 mg/kg bw) resulted in decreased plasma alkaline phosphatase in females, decreased apolar retionoids in female livers and increased CYP19/aromatase activity in the ovaries (van der Ven 2009).

Rats exposed to HBCD gave effects on phase I and II enzymes (CYP3A3 and UGT), lipid metabolism and cholesterol biosynthesis. A more efficient elimination process of HBCD in males was registered (Canton 2008).

Rat microsomes exposed to HBCD gave an mRNA induction in CYP2B1 and CYP3A4, probably via PXR and CAR signalling pathways. Higher enzyme induction in females than in males (Germer 2006).

Chicken hepatocytes exposed to HBCD gave effects on the mRNA level on the lipid regulation, the thyroid hormone pathway and phase I and phase II enzymes (L-FABP, THRSP, TTR, CYP2H1, CYP3A37 and UGT1A9) (Crump 2008).

Juvenile Rainbow Trout exposed to HBCD had effects on biotransformation enzymes (reduced CYP1A1 activity and induced glucuronosyltransferase (UDPGT) activity). All diastereomers (α-, β- and γ-) showed effects, with some differences in levels (Palace 2008).

Thyroid effects

The main endocrine disrupting effect of HBCD is on the thyroid hormone metabolism and the hypothalamo-pituitary-thyroid axis.

Thyroid hyperplasia was observed in both sexes in a rat study with HBCD at 940 mg/kg/day (Zeller and Kirsch 1969). Thyroid and pituitary weight was increased in female rats in a study using HBCD from 0-200 mg/kg/day (van der Ven 2006). No thyroid effects were observed in a recent rat study using HBCD from 0-100 mg/kg/day (van der Ven 2009).

Serum T4 was decreased and TSH was increased in female rats in a study using HBCD at 0-200 mg/kg/day (van der Ven 2006).

In the presence of T3 (50 ng/ml), HBCD (3.12, 6.25, 12.5 and 25 µM) increased Thyroid receptor (TR)-mediated gene expression in HeLaTR cells (Yamada-Okabe 2005).

Exposure of *Xenopus laevis* tadpole tail tips to 1000 nM HBCD in combination with 20 nM T_3, potentiated tail tip regression with 35% +/- 5% (Schriks 2006).

HBCD significantly enhanced the number of proliferating cells in the brain of *Xenopus Laevis* tadpoles at the two highest doses 100 and 1000 nM (in combination with 1 nM T3) with 33.2 % and 24.5 %, respectively (Schriks 2006).

Juvenile Rainbow Trout exposed to HBCD gave a transient disruption of the thyroid axis (reduced T4ORD activity (Deiodinase: T4->T3), lower FT4 activity, higher FT3 activity). All diastereomers (α-, β- and γ-) showed effects, with some differences in levels (Palace 2008).

Steroid hormone receptor effects

Rat pituitary cells exposed to exhibits antiandrogenic (AR) (γ-HBCD, IC50 = 3.7 µM), antiprogesteronic (PR) (γ-HBCD, IC50 = 1.4 µM), T_3-potentiating properties (α-HBCD and γ-HBCD) and a low binding to transthyretin (TTR) to compete with T4 (α-HBCD and β-HBCD, EC_{50} = 12-15 µM) (Hamers 2006).

HepG2 cells exposed to HBCD (0.03–0.3 ng/ml) resulted in inhibition of mRNA expression of two oestrogen responsive genes (ERα and THRα) (Aniagu 2008).

Reproduction Toxicology

Developmental toxicity

Two ordinary developmental toxicity studies have failed to demonstrate any fetotoxicity, teratogenic potential or adverse effects from HBCD on development of rats. 0-750 mg/kg/day (n=20) and 0, 500 or 1000 mg/kg/day (n=25) was given orally (Murai, Kawasaki & Kanoh 1985 and CMA & Chemical Manufacturers Association Brominated Flame Retardant Industry 1999).

Fertility

The available data from rats indicate effects on reproductive organs only at high exposure levels. But the high bioaccumulation of HBCD and the potential for milk transport are reasons to investigate further the full life-time toxicity. Recent data in a human study shows effects on the sexual development from lower levels of HBCD.

A two-generation reproductive toxicity study in 24 rats (F0) was given 0, 150, 1500 or 15000 ppm HBCD (Ema 2008). Effects were not found on sex hormone-dependent events. Changes were found on the thyroid hormone axis (T4, TSH, FSH), liver enzymes (CYP2B1 and CYP2B2), liver size in (females). Results suggest that HBCD is potentially reproductively toxic, but no adverse effects on reproductive parameters in F1 dams or F2 pups were noted. The NOAEL was 10.2 mg/kg bwt/day = 150 ppm which is far below estimated human daily intake.

A recent study in the Netherlands shows effects of prenatal exposure of HBCD on sexual development in healthy infants (Meijer 2008). Sex hormone levels like luteinizing hormone and testosterone were influenced from prenatal exposure (n=21-33). Testes volume and penile length were also affected from prenatal exposure (n=36).

A recent study on rats showed reproductive effects of HBCD (0-100 mg/kg bw), like increased CYP19/aromatase activity in the ovaries (n=2) and also decreased weight of the testis (n=10) (van der Ven 2009).

Developmental neurotoxicity

Neonatal HBCD exposure may cause developmental neurotoxic effects due to observed statistically significant changes in spontaneous behaviour, learning and memory defects in two rat studies (0.9 or 13.5 mg/kg bw and n=10 or 0-100 mg/kg bw). A LOAEL of 0.9 mg/kg/day was determined, but this needs to be confirmed by other laboratories (Eriksson 2006). A recent human study of prenatal exposure has shown effects on psychomotor development (Meijer 2008).

Neurotoxicology

Neurotransmitter effects

HBCD inhibit the plasma membrane uptake of glutamate and dopamine (IC50 = 4µM) and the vesicular uptake of dopamine (IC50 = 3µM) (Fonnum 2006, Mariussen and Fonnum 2003).

Exposure to HBCD (0-20 µM) dose-dependently inhibits depolarization-induced increase in calcium levels and neurotransmitter release in a neuroendocrine *in vitro* model using rat pheochromocytoma (PC12) cells (Dingermans 2008).

Other effects

Increased IgG response in males, increased fraction of neutrophilic granulocytes in males, decreased trabecular bone density of tibia in females was found in a recent study on rats using HBCD (0-100 mg/kg bw), (female rats, n=2) (male rats, n=10) (van der Ven 2009).

Zebrafish exposure to HBCD gave increased Hsp70 (heat shock protein) and SOD (superoxide dismutase) EC/LC50 > 100 mg/l (Hu 2008).

HepG2 cells were exposed to HBCD (0.5–10 µg/ml) and cell viability was measured (Zang 2008). γ-HBCD was more cytotoxic than β-HBCD that was more cytotoxic than α-HBCD. The (+) enantiomers were more cytotoxic than the (-) enantiomers.

Mutagenicity

The evidence from available studies indicates that HBCD lacks significant genotoxic potential *in vitro* as well as *in vivo* (TSCATS 1990e, TSCATS 1990a, Gudi and Schadly 1996, BASF 2000 and HBCD Risk Assessment, EEC, April 2007). HBCD induces genetic recombination in *in vitro* assays in mammalian cells indicating a potential to cause cancer via a non-mutagenic mechanism (Helleday 1999), but the relevance of the study is considered questionable due to lack of relevant information and low recombination activity (Ausgabe 2001).

Carcogenicity

No adequately performed HBCD cancer study has been reported. On long-term study with restricted validity in 50 male and 50 female mice, no evidence of carcogenicity was found in doses up to 1,300 mg/kg bwt/day (Kurokawa 1996 and HBCD Risk Assessment, EEC, April 2007).

Gender aspects

At long-term exposure, higher concentrations of HBCD in fat tissue are achieved in females than in males, but the substance is bioaccumulating in both sexes.

Fat tissue levels of HBCD 20 male and 20 female rats (0 or 1000 mg HBCDD/kg/day orally for up to 90 days) (Chengelis 2001). The highest concentration of α-HBCDD in both sexes was at day 89, with mean levels of 3101 µg/g fat for males and 4342 µg/g fat for females.

The excretion of γ-HBCDD was investigated in 8 female and 2 male rats after an oraldose (Yu & Atallah 1980).

Rat microsomes exposed to HBCD gave an mRNA induction in CYP2B1 and CYP3A4, more in females than in males (Germer 2006).

Rats exposed to HBCD gave effects on phase I and II enzymes (CYP3A3 and UGT), lipid metabolism and cholesterol biosynthesis (Canton 2008). A more efficient elimination process of HBCD in males was registered.

HBCD exposure in male and female rats (0-100 mg/kg bw) resulted in decreased plasma alkaline phosphatase in females, decreased apolar retionoids in female livers, increased CYP19/aromatase activity in the ovaries, increased IgG response in males, increased fraction of neutrophilic granulocytes in males, decreased trabecular bone density of tibia in females (female rats, n=2) (male rats, n=10) (van der Ven 2009).

NOAEL

The HBCD substance tested has a very low acute toxicity by oral and dermal exposure, and it has not been possible to determine a LD50 value. The minimum oral lethal dose is > 20 g/kg in rats (Wilson and Leong 1977 and Lewis and Palanker 1978), and > 40 g/kg in mice (EPA 1990 and Tobe 1984). LD_{50} of dermal exposure is > 20 g/kg in rabbits (Wilson and Leong 1977 and Lewis and Palanker 1978). The acute toxicity by inhalation has not been investigated properly, but seems to be low.

From a study measuring fetotoxic and teratogenic potentials, a foetal and maternal NOAEL of 1000 mg/kg/day was determined (CMA & Chemical Manufacturers Association Brominated Flame Retardant Industry 1999).

The effects on the liver, especially in the female rats, indicate a LOAEL of 125 mg/kg/day (Chengelis 1997).

From observing effects on liver, thyroid and prostate in rats, a LOAEL = 10-20 mg/kg/day was concluded (Chengelis 2001).

From measuring liver enzyme induction in female rats, the NOAEL/BMD-L of 22.9 mg/kg/day is proposed (van der Ven 2006). The same authors proposed Benchmark doses (BMD-L) for female rats: for the increased thyroid weight a BMD-L of 1.6 mg/kg/day, for the liver enzyme for T4-conjugation (T4-UGT) a BMD-L of 4.1 mg/kg/day, for the increased pituitary weight in female rats a BMD-L of 29.9 mg/kg/day.

From a two-generation reproductive toxicity study in rats, the NOAEL was set to 10.2 mg/kg bwt/day = 150 ppm which is far below estimated human daily intake (Ema 2008).

From a study of neonatal male NMRI mice, a LOAEL of 0.9 mg/kg/day was determined, but this needs to be confirmed by other laboratories (Eriksson 2006).

HBCD inhibited plasma membrane uptake of glutamate and dopamine (IC50 = 4 µM) and the vesicular uptake of dopamine (IC50 = 3µM) (Fonnum 2006, Mariussen and Fonnum 2003).

Modes of action

Several endpoints for HBCD effects have been analysed lately, such as enzymatic, endocrinologic and histopathologic. The only really consistent effect was liver weight increase in female rats, and in most studies also in male rats. Hepatic enzyme induction is clearly involved and likely the cause of weight increase. Studies of the thyroid system have shown either effect in both sexes, only in females, or no effects (HBCD Risk Assessment, EEC, April 2007). Decreased serum thyroxine (T4) and increased serum TSH was observed (Chengelis 2001, Germer 2006 and van der Ven 2006). Similar thyroid hormone (TH)-related effects were seen in a two-generation study in rats (Ema 2008), and in addition reproduction related effects such as histology of the ovary and viability of the pups.

Changes in liver and thyroid hormone system and prostate could possibly be explained by enzyme induction in the liver, since hepatic glucuronidation enzymes like T4-UGT transferase is known to be the rate limiting step in the biliary excretion of T4 (HBCD Risk Assessment, EEC, April 2007). T4-UGT transferase involved in the metabolism of T3/T4 is induced by HBCD in both sexes (van der Ven 2006). A hypothesis that could be supported from studies in female rats is that the first effect is an enzyme induction followed by an activation of the pituitary (resulting in TSH synthesis), and followed by an activation of the thyroid (hyperactive cells/weight increase) and finally if the T4/T3 decreases it can have effects other tissues and systems (HBCD Risk Assessment, EEC, April 2007).

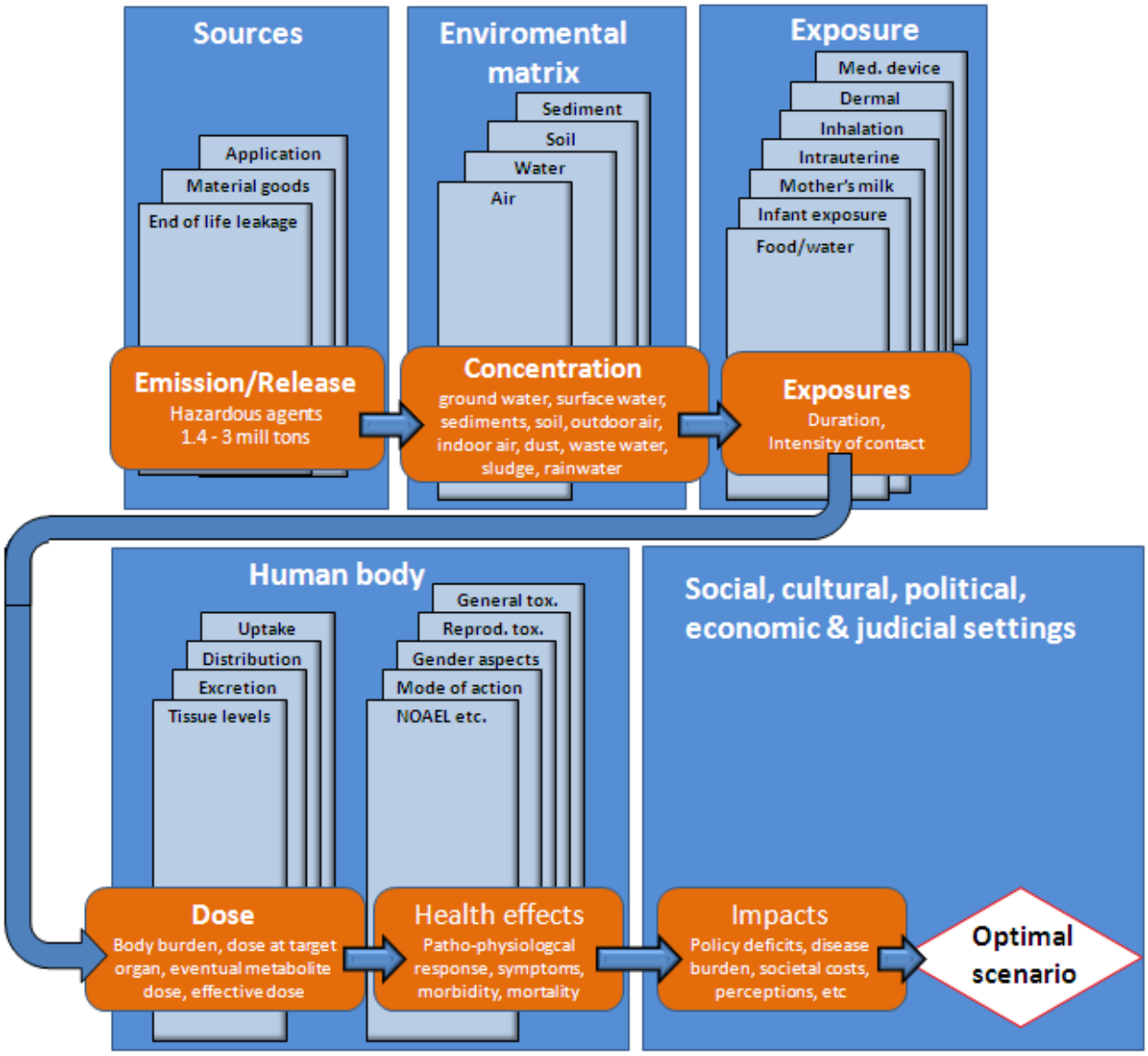
Another hypothesis is that instead of affecting the thyroid system via hepatic enzyme induction, HBCD acts via steroid hormone receptors like the progesterone receptor and the androgen receptor where HBCD exerts antagonistic effects (Hamers 2006).

Also, binding of HBCD to thyroxine binding transport protein (TTR) could displace T4 from TTR, making T4 more susceptible to metabolism and excretion (Hamers 2006, Yamada-Okabe 2005, Schriks 2006).

Developmental neurotoxicity was observed in mice (Eriksson 2006), and in humans (Meijer 2008), and possible roles of neurotransmitter inhibition has been shown (Dingermans 2008, Fonnum 2006 and Mariussen and Fonnum 2003).

Altogether these effects point towards a possible role of HBCD as a (neuro-) endocrine disruptor affecting the hypothalamo-pituitary-thyroid axis.

PHTHALATES: PART A. EVALUATION OF THE STRUCTURE AND COMPLETENESS OF THE CAUSAL DIAGRAM



Does the diagram take into account all of the important parameters when evaluating the risks related to production, use and discharge of phthalates? **YES/NO**

If No, please explain:

Are the different causal relationships adequately structured? **YES/NO**

If No, please explain:

Are there any unnecessary parameters shown in the diagram that could be deleted? **YES/NO**

If Yes, please explain:

PART B. EVALUATION OF INDIVIDUAL CAUSAL ELEMENTS

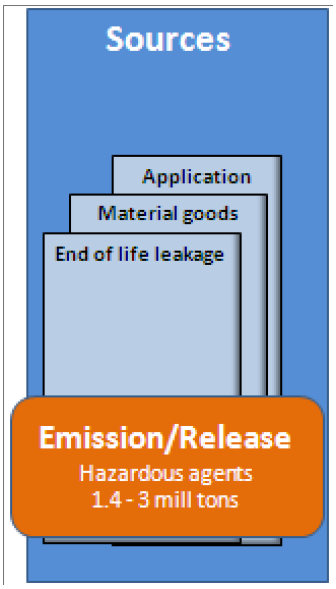
In the questions that follow you will be asked to express your confidence in scientist's ability to predict the concentrations, exposure and effects of phthalates. Insert a check mark where you feel it is appropriate.

It is important that you consider each question **independently** from the others. When answering a question do not take into account the state of knowledge in previous/other questions. As an annex to this questionnaire, you will find summary information related to individual questions, based on HENVINET scientific review to be published soon.

The experts are asked to express their level of confidence according to the guidelines below.

4. Very high confidence. At least a 9 out of 10 chance of being correct.	3. High confidence. At least an 8 out of 10 chance of being correct.	2. Medium confidence. At least a 5 out of 10 chance of being correct.	1. Low confidence. At least a 2 out of 10 chance of being correct.	0. Very low confidence. Less than a 1 out of 10 chance of being correct.

Sources

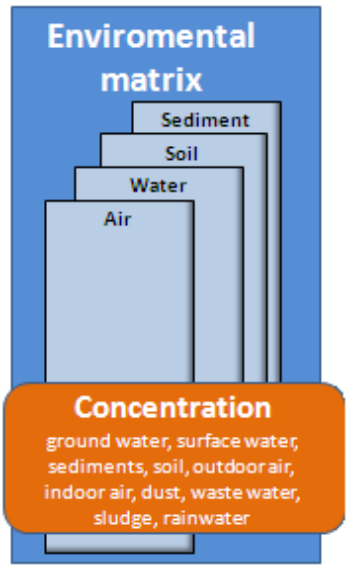


1. What is your level of confidence in our data on the production volumes of phthalates?

2. What is your level of confidence in our ability to predict the magnitude of emission/release/leakage phthalates during production, transport and use?

3. What is your level of confidence in our ability to identify and quantify all different applications of phthalates?

Environmental matrix



4. What is your level of confidence in our ability to predict the concentration of phthalates in groundwater?

5. What is your level of confidence in our ability to predict the concentration of phthalates in sediments?

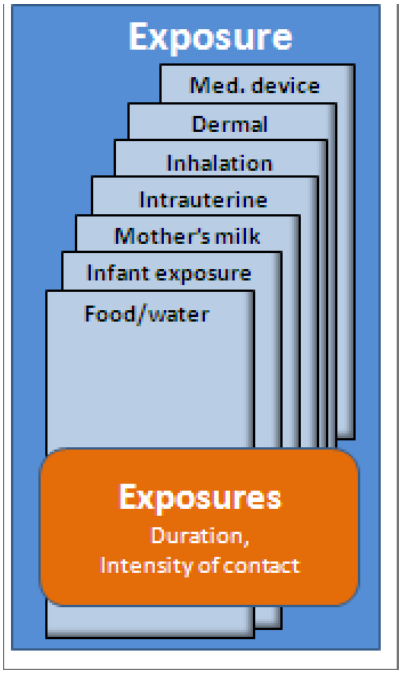
6. What is your level of confidence in our ability to predict the concentration of phthalates in soil?

7. What is your level of confidence in our ability to predict the concentration of phthalates in outdoor air?

8. What is your level of confidence in our ability to predict the concentration of phthalates in indoor air and dust?

9. What is your level of confidence in our ability to predict environmental transformation and biological half-lives for phthalates?

Exposure



10. What is your level of confidence in our ability to predict the *levels of exposure* to phthalates in the *general* populations?

11. What is your level of confidence in our ability to predict the *main sources of exposure* to phthalates for the *general* population?

12. What is your level of confidence in our ability to identify and predict the *levels of exposure* to phthalates in highly exposed *groups* in the population?

13. What is your level of confidence in our ability to identify and predict the *main sources of exposure* to phthalates in highly exposed *groups*?

14. What is your level of confidence in our ability to predict the *levels of oral exposure* to phthalates in the *general population*?

15. What is your level of confidence in our ability to predict the *levels of oral exposure* to phthalates in highly exposed *groups*?

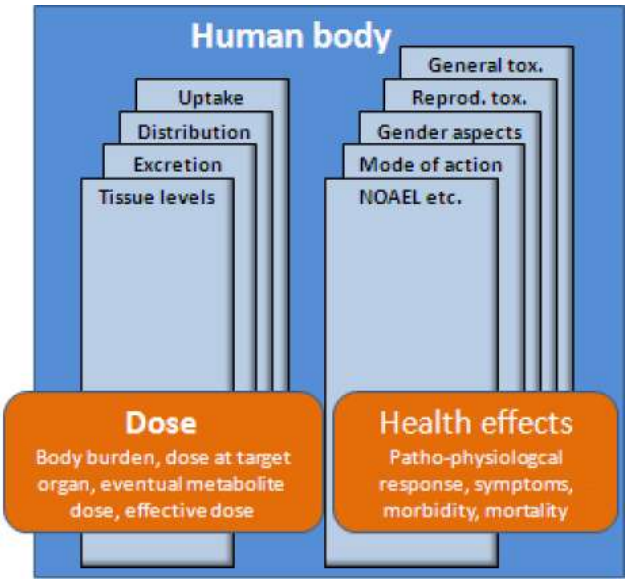
16. What is your level of confidence in our ability to predict the *levels of inhalational exposure* to phthalates in the *general population*?

17. What is your level of confidence in our ability to predict the *levels of inhalational exposure* to phthalates in highly exposed *groups*?

18. What is your level of confidence in our ability to predict the *levels of dermal exposure* to phthalates in the *general population*?

19. What is your level of confidence in our ability to predict the *levels of dermal exposure* to phthalates in highly exposed *groups*?

Toxicokintetics, toxicology and health effects



20. What is your level of confidence in our ability to predict the final concentrations in the target tissues, taking factors such as absorption, distribution, metabolism and excretion into consideration?

21. What is your level of confidence in our ability to predict differences in toxicokinetics, in view of identifying sensitive groups (age, gender etc)?

22. What is your level of confidence in our ability to predict adverse health effects in humans caused by environmental exposure to phthalates?

23. What is your level of confidence in our ability to predict that only/mainly ortho-phthalates (DEPH, DBP, BBP) have the potential to cause detrimental health effects?

24. Based on experimental studies, what is your level of confidence in our ability to predict adverse health effects caused by phthalates in

a) Males? b) Females?

25. What is your level of confidence in our ability to predict the NOAEL of

a) Single ortho-phthalates? b) Mixtures of phthalates?

26. What is your level of confidence in out knowledge on the mechanism(s) of action of

a) Phthalates and b) their metabolites?

27. What is your level of confidence in the validity of the claim that phthalates and/or their metabolites cause endocrine disrupting effects in

a) The reproductive system b) The thyroid system?

c) The metabolic system? d) Overall assessment

28. What is your level of confidence in our ability to predict harmful effects of phthalates in the environment and applications on human health?

28. Final comments

Are there any comments you would like to make in closing to complete your evaluation? Perhaps you would like to comment on key areas of knowledge which you think are underdeveloped? Perhaps you would like to provide your impressions of the usefulness of this evaluation, or provide suggestions on how to improve it?

REVIEW BASED BACKGROUND INFORMATION

Sources

What is your level of confidence in our data on the production volumes of phthalates?

*The total annual global production of all phthalates is estimated to be 3x10*6 tons, of which 2/3 is DEHP.*

What is your level of confidence in our ability to predict the magnitude of emission/release/leakage phthalates during production, transport and use?

Phthalate esters and their metabolites are constantly detected in the indoor environment, consumer products, human urine, mother's milk and amniotic fluid.

Phthalates incorporated in PVC are not covalently bound and are therefore easily released into the environment.

What is your level of confidence in our ability to identify and quantify all different applications of phthalates?

Uses of various phthalates depend on their molecular weight (MW):

Higher MW phthalates such as DEHP, DiNP and DiDP are used as plasticizers to impart flexibility and durability in polyvinylchloride (PVC) products in construction material, clothing and furnishing.

Low MW phthalates such as DEP, DMP and DBP are used as solvents in cosmetics, insecticides, pharmaceuticals, construction materials, car products, clothing, food package, children products and medical devices.

Environmental matrix

What is your level of confidence in our ability to predict the concentration of phthalates in groundwater?

Reported DEHP concentrations in ground water from the United States were reported as mean 15.7µg/l, range nd-470µg/l, while concentrations in Europe were 0.26µg/l with a range from <0.07µg/l to 1.4ug/l. Concentrations for drinking water in Europe ranged from <0.18µg/l to 3.5µg/l. Sample sizes were in the range from 2 to 9 samples investigated.

What is your level of confidence in our ability to predict the concentration of phthalates in sediments?

DEHP concentration in sediments from Europe were found to be generally low with mean measurable reported concentrations of 4.9µg/g (range: 0.0001-487µg/g; n=405)

Microorganisms present in the sediments are responsible for the major routes of breakdown of DEHP

Sediment fingerprints of phthalates showed good correlation with per capita consumption for the high molecular phthalates.

What is your level of confidence in our ability to predict the concentration of phthalates in soil?

Reported levels for DEHP from European countries were 48 µg/kg mean with a range of 4-5100 (n=3). In the US comparable concentrations ranged from 0.03µg/kg to 1280µg/kg (data points 1)

What is your level of confidence in our ability to predict the concentration of phthalates in outdoor air?

Concentrations of DEHP measured in Europe show a mean level of 21.9 ng/m^3 and a range of >0.28-1090 ng/m^3 (n=85).

DEHP concentrations were found to be 1000 times lower in outdoor than in than indoor air in a Japanese study

Air concentrations were found to be higher in summer than in winter, probably due to enhanced vaporization from plastics.

Atmospheric transport is important for the presence of phthalates in the Arctic

What is your level of confidence in our ability to predict the concentration of phthalates in indoor air and dust?

Phthalates and their metabolites are constantly detected in the indoor environment.

Indoor air DEHP concentrations are found to be up to 1000 times higher than in outdoor air and reached a maximum of 3.13ug/m^3. The air in 27 houses around Tokyo was measured in the study.

However, studies from Europe showed a mean indoor air concentration for DEHP of 245 ng/m^3 with a range of 18-1046 ng/m^3 (n=398). The levels in dust were found to be within a range of 0.002-4.58 g/kg and have a mean concentration of 0.62 g/kg (n=55).

A Norwegian study found higher concentrations of DBP in indoor dust of different particle sizes than DEHP. The concentration varied a 10-fold between different sample sites.

PVC floors are a potential source for phthalates in indoor air; however, PVC-coated wall coverings are found not to release sufficient quantities to lead to intake in the range of the acceptable daily intake (ADI) values.

What is your level of confidence in our ability to predict environmental transformation and biological half-lives for phthalates?

Phthalates monoesters have a biological half-life of approximately 12hrs.

Microorganisms present in sediments provide a major route of breakdown of DEHP

Degradation half-life of DEHP in wastewater is 1.6 days.

Exposures

What is your level of confidence in our ability to predict the *levels of exposure* to phthalates in the *general* populations?

DEHP exposure was estimated in 2000 to be 3-30 µg/kg body weight / day for adults, 2-3 times higher for children.

More than 90% of the estimated DEHP intake for adults is from food, whereas formula-fed and breast-fed babies retain only 44% and 60% of the total DEHP from food.

Reduction of DEHP exposure by 40% from 1996 – 2003 in Germany.

Median total intake of DEHP range from 8.2µg/kg bw/day in adults up to 25.8µg/kg bw/day in toddlers.

The secondary DEHP metabolites in urine give a more accurate estimate of the DEHP exposure than the primary monoester.

What is your level of confidence in our ability to predict the *main sources of exposure* to phthalates for the *general* population?

The main source of exposure for the general population is through ingestion of contaminated food through production and packaging.

What is your level of confidence in our ability to identify and predict the levels of exposure to phthalates in highly exposed groups in the population?

Children:

Breast milk contained 0.062 ug/g DEHP

Baby food levels were 0.36-0.63 µg/g food.

Infant formula levels were 0.04-0.06 µg/g food.

Infants consuming formula are estimated to be exposed to 8-13 µg/kg bw/day.

Infants fed on breast milk are estimated to be exposed to 8-21 µg/kg bw/day.

It was estimated that a 3 kg child will get 2.5-16.1 µg/kg bw/day, which is well below the European Commission TDI of 37 µg/kg bw/day.

Exposure from toys is estimated to be 1.74 µg/min/10 cm^2.

Medical patients:

Exposure from medical devices is estimated to be:

From parenteral nutrition -> 4-20 mg/day of DEHP is leaching from tubings.

From respiratory therapies-> lower than the detection limits.

From blood transfusions -> > 4 mg/kg bw/day of DEHP (FDA)

From donating and receiving platelets -> 48.1 µg/kg bw

From dialysis -> 59.6 mg during a 4-hour dialysis.

From medication-> exceeded the TDI 4-fold after intake of only four tablets.

Industrial workers:

PVC flooring material increased the air concentrations for the first 150 days after which concentration tended to level off at approximately 1ug/m^3.

Women in reproductive age between 20 and 40:

Exposure can occur from different beauty products (Data from USA).

What is your level of confidence in our ability to identify and predict the *main sources of exposure* to phthalates in highly exposed *groups*?

Beauty products that contain DBP, such as deodorants, perfumes, hair gels, hair sprays, nail polish and body lotions -> Women in reproductive age between 20 and 40 years using cosmetics are exposed.

Ingested, inhaled or absorbed phthalates from the mother -> Fetus are exposed through placenta (rodent studies).

Ingested, inhaled or absorbed phthalates from the mother -> Newborns are exposed through lactation (rodent and human studies).

Toys and child care articles containing phthalates, mainly DEHP, DBP, BBP and DiDP Four is mentioned (All three are now banned by EU. USA has permitted use of DiNP) -> Children between 0.5 – 4 years of age that mouth, suck or chew on toys are exposed.

Baby care products, such as lotion, powder and shampoo -> Babies are exposed.

Factories producing unfoamed PVC flooring -> Industrial workers are exposed.

Medical devices for administration of medicine and nutrients used during blood transfusions and haemodialysis, may contain very high DEHP levels (20-40%) -> Individuals undergoing medical interventions are exposed.

Certain pharmaceuticals coated with phthalates, such as antibiotics, antihistamines and laxatives -> Patients taking the drugs are exposed.

What is your level of confidence in our ability to predict the *levels of oral exposure* to phthalates in highly exposed *groups* and the *general population*?

Oral ingestion of phthalates originates from contaminated food, mothers milk and toys.

The general dietary intake of DEHP and DBP is estimated to be highest in infants and children between 1-6 years and the exposure is in the range of the tolerable daily intake (TDI) (0.05 mg/kg/day).

More than 90% of the estimated DEHP intake for adults is from food, whereas formula-fed and breast-fed babies retain only 44% and 60% of the total DEHP from food.

Studies in rodents show that phthalates are rapidly absorbed from the intestine, and as much as 90% were detected in urine afterwards. Male human studies show that 67% was excreted in the urine.

Prepacked food increases the levels. In Japan 11.8 ug/g DEHP were detcted in prepacked food.

Heating of prepacked food in a microwave resulted in 92.2% of the TDI of DEHP.

Total diets of adults in Denmark in 2000 contained less than 0.188 ug/g DEHP? resulting in a minimum and maximum daily intake of 2.7 and 4.3 ug/kg bw/day.

A more recent study in Germany resulted in a daily intake of DEHP with a range between 1.0 and 4.2 ug/kg bw/day.

Exposure from toys is estimated to be 1.74 ug/min/10 cm3.

What is your level of confidence in our ability to predict the *levels of inhalational exposure* to phthalates in highly exposed *groups* and the *general population*?

Phthalates are absorbed after inhalation in humans.

Indoor air concentration is 3.13 ug/m^3 (DEHP measured in Japan).

Exposure from building materials is maximum 3.1 ug/m^3.

PVC flooring material increased the air concentrations for the first 150 days after which concentration tended to level off at approximately 1 ug/m3.

DEHP accounted for more than 80% of the phthalate concentration of household dust of 703 mg/kg (median) and 1763 mg/kg (maximum).

Indoor DEHP concentrations ranged from 156 ng/m^3 to 458 ngn/m^3 in kindergartens.

DEHP dust concentrations and children with doctor-diagnosed asthma were significantly correlated (Swedish study).

What is your level of confidence in our ability to predict the *levels of dermal exposure* to phthalates in highly exposed *groups* and the *general population*?

No human *in vivo* dermal absorption studies are available.

In vitro comparisons show that absorption occurs more rapidly through rat skin than human skin.

In guinea pigs only 3% and 21% was absorbed and excreted after 1 and 7 days, respectively.

Toxicokinetics

What is your level of confidence in our ability to predict the final concentrations in the target tissues, taking factors such as absorption, distribution, metabolism and excretion into consideration?

Most data are gained from animal studies, human data are scarce.

There is high variability between species in toxicokinetics.

No significant accumulation of phthalates in organs and tissues, less than 1% retained.

Distributed throughout the body with the blood to all tissues.

Highest concentrations of DEHP have been measured in liver and kidney.

The orally ingested di-ester phthalates are metabolized into monoesters by non-specific esterases and lipases, and then further by various oxidation and hydroxylation reactions resulting in secondary metabolites.

Most of the orally ingested phthalates (70%) are excreted in the urine as secondary metabolites in a male human study, and only 13% is excreted as primary monoesters.

Secondary metabolites are more accurate biomarkers of exposure, compared to the primary monoesters, since the secondary metabolites account for most of the excreted phthalates.

What is your level of confidence in our ability to predict differences in toxicokinetics, in view of identifying sensitive groups (age, gender etc)?

Exposure studies in humans measuring primary and secondary metabolites suggest age-related differences in metabolism and/or clearance.

Premature and term infants have reduced renal clearance, due to lack of glucuronidation pathways, which may increase the internal dose of toxic metabolites. Also human neonates have less pancreatic lipases.

Sex and ethnicity does not matter for toxicokinetics of phthalates.

High inter-species variability exists in the first step of biotransformation (lipases) of phthalates.

Toxicology/ Health effects

Based on experimental studies, what is your level of confidence in our ability to predict adverse health effects caused by phthalates in

Males?

Females?

Effects of exposure are best studied in males; however, a few studies also look at female reproduction.

Pathological changes in male reproductive organs and lower testosterone levels have been observed when the animal is exposed prenatally (50 mg/kg DBP or 10 mg/kg DEHP). Increased testosterone levels are seen after postnatal exposure (10 mg/kg bw/day from PND 21-120).

Reduction of prenatal maternal weight gain and number of pups and increase in postnatal mortality has been observed after exposure to high doses (750 and 1500mg/kg bw/day from GD 3-PND 21). Increased nipple sizes in male offspring were seen at all dose levels (375-1500 mg/kg bw/day) and are also seen in other studies, while accessory reproductive organ developmental effects seen at highest doses. No effects seen in female offspring of this study.

Reduction of Sertoli cell proliferation and increase in multinucleated germ cells and interstitial hyperplasia, depletion of germinal tubule and decreased seminiferous tubule diameter are findings in lower doses (>100 mg/kg single dose, 100-500 mg/kg bw/day) when exposed during development.

Low doses (14-23 mg/kg bw/day) have caused small reproductive organ sizes in F1 and F2 generations of male rats, without any histological changes or other adverse reproductive effects.

Effects on male reproductive organs are similar in animals exposed to a single dose and animals exposed to multiple doses during pre- and postnatal development.

In females, exposure to DEHP before and during puberty (>=500 mg/kg bw/day) increased serum estradiol, advanced onset of puberty and increased ovarian and uterine weight in marmosets, while also lower doses of 2 mg/kg decreased levels of estradiol and led to disturbances of normal ovarian function in adult rats.

What is your level of confidence in our ability to predict adverse health effects in humans caused by environmental exposure to phthalates?

Few studies have reported a relationship between environmental exposure and human health.

Animal studies support the hypothesis that there is a relationship between environmental exposure and human health.

Effects observed in rat studies resemble testicular dysgenesis syndrome in humans

Levels of phthalates have been negatively associated with sperm parameters and testosterone and LH concentrations.

In females, higher levels of phthalates have been associated with endometriosis in a few studies.

In human boys of 2-36 months of age, a negative association between anogenital distance and phthalate metabolites in their mothers' urine has been detected.

What is your level of confidence in our ability to predict the NOAEL of

Single ortho-phthalates?

Mixtures of phthalates?

The Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTTEE) support the suggested new NOAEL of DEHP of 4.8 mg/kg bw/day for testicular and developmental toxicity, which was found to be the most sensitive endpoint (2004).

The same committee recommended using not only MEHP, but also 5-OH-MEHP and 5-oxo-MEHP for biomonitoring

Sensitivity in different species seems to differ considerably. E.g. in mamorsets no testicular effects were seen at a dose of 2500 mg/kg bw/day. This is explained by a lower absorption from marmoset intestines than from rodent intestines. Rodent liver peroxisome proliferation is regarded not relevant for human risk assessment as rodents are highly sensitive to this phenomenon and that the critical effects of DEHP relate to reproduction.

A few experimental studies in rats published after 2005 suggest a similar mechanism of action for DEHP, BBP, DBP and DiBP on foetal testicular testosterone production and for DiBP, DEHP, DBP and DiNP on foetal testicular testosterone production and testicular histopathology, but this has not been related to other effects

What is your level of confidence in our knowledge of the mechanism(s) of action of

Parent phthalate compounds?

Phthalate metabolites?

A study has shown that only unmetabolized phthalates have affinity for steroid receptors, not the absorbed monoesters. This indicates a lack of receptor-mediated effects in vivo.

MEHP has shown to be a more potent testicular toxicant than the parent compound DEHP. MEHP readily crosses the placenta

Reduced testosterone concentration following DEHP or DBP might be due to reduced expression of genes involved in steroidogenesis. Phthalates also interfere with expression of other genes involved in testicular descent and cell cycle, causing decreased proliferation, eg of Sertoli cells.

Peroxisome-proliferatior-activated receptors (PPAR), which are involved in metabolism, cell growth and stress responses, may be involved in testicular toxicity following phthalate exposure. PPAR is probably also responsible for reduced levels of aromatase and thus estradiol.

What is your level of confidence in the validity of the claim that only/mainly ortho-phthalates (DEHP, DBP and BBP) have the potential to cause detrimental health effects?

The general consensus is that only ortho-phthalates with side-chain length of C4-C6 including DEHP, DBP and BBP have potential to disrupt normal development and reproduction.

Findings have suggested that these phthalates are endocrine disruptors affecting development, reproductive and thyroid hormonal axes and may contribute to the increase in prevalence of metabolic syndrome.

Few studies with the other phthalates are available.

What is your level of confidence in the validity of the claim that phthalates and/or their metabolites cause endocrine disrupting effects in

The reproductive system

The thyroid system?

The metabolic system?

Pathological changes in male reproductive organs and lower testosterone levels have been observed when the animal is exposed prenatally (50 mg/kg DBP or 10mg/kg DEHP). Increased testosterone levels are seen after postnatal exposure (10 mg/kg bw/day from PND 21-120).

Increased nipple sizes in male offspring were seen at all dose levels (375-1500 mg/kg bw/day) and are also seen in other studies, while accessory reproductive organ developmental effects seen at highest doses

Reduction of Sertoli cell proliferation and increase in multinucleated germ cells and interstitial hyperplasia, depletion of germinal tubule and decreased seminiferous tubule diameter are findings in lower doses (>100 mg/kg single dose, 100-500 mg/kg bw/day) when exposed during development

Low doses (14-23 mg/kg bw/day) have caused small reproductive organ sizes in F1 and F2 generations of male rats, without any histological changes or other adverse reproductive effects.

In females, exposure to DEHP before and during puberty (>=500 mg/kg bw/day) increased serum estradiol, advanced onset of puberty and increased ovarian and uterine weight in marmosets, while also lower doses of 2 mg/kg decreased levels of estradiol and led to disturbances of normal ovarian function in adult rats

Effects observed in rat studies resemble testicular dysgenesis syndrome in humans

Levels of phthalates have been negatively associated with sperm parameters and testosterone and LH concentrations.

In females, higher levels of phthalates have been associated with endometriosis in a few studies.

In human boys of 2-36 months of age, a negative association between anogenital distance and phthalate metabolites in their mothers' urine has been detected.

Normal thyroid hormone function has been shown to be important for reproductive system development in females and males.

Thyroid hormone and TSH levels were inversely correlated with urinary MEHP concentration in humans and animal studies also indicate an association between DEHP exposure and thyroid hormones.

Significant positive correlations between waist circumference and urinary phthalate metabolites are found in American men.

ANNEX 2: ALL AVAILABLE EVALUATION RESULTS

TOPIC 1: ASTHMA AND ALLERGIES

CLIMATE CHANGE: PART A - EVALUATION OF THE STRUCTURE AND COMPLETENESS

1. Does the diagram take into account all of the important parameters when evaluating the asthma and allergy risks related to climate change? If no, please explain. (17 experts)

8 experts replied YES, 9 replied NO. the different suggestions give by 7 of 17 experts were:

- Susceptible groups defined by genetic factors are not considered. These subgroups may be at extra risk of disease or exacerbation when exposed to a certain environmental factor.
- Changes in the level and composition of air pollution, such as a modified size spectrum of particles (due to changes in air humidity) and increased and new emissions of indoor air pollutants (from furniture and building materials)
- Changes in the atmospheric stability that is a precondition for the accumulation of pollutants; the expected increase in temperature can be associated with (i) an intensification of weather changes and this reduces atmospheric stability and (ii) an aggravation of heat episodes that often occur with high pressure weather situations and have a very stable atmosphere.
- Abrupt changes in weather might overstrain the adaptation of the human body and this can result in infections; the latter are more or less related with allergies and can exacerbate symptoms of protect against allergy.
- The economic impact of climate change and possible increased immigration are other factors that have to be taken into account. Economic consequences of the climate change may worsen the situation. Increased migration due to climate change may also be a factor to take into account
- Pests and vermins growth might be also affected by climatic change; Ventilation activities and potential air conditioning were missing.
- The diagram covers a large number of factors possibly related to climate, and because of this also possibly related to climate change, and as a next step possibly related to respiratory health. But one main problem is that there is not a clear association between climate and asthma prevalence/incidence within the existing gradients of climate globally. Probably some factors related to climate change might also be beneficial for asthma, but this is hard to know (less exposure to cold air, more microbial exposure in childhood etc)
- Impact of thunderstorms on asthma exacerbations.
- The impact of climate change to psychosocial stress could be also taken into account; a dysregulated stress response could result in asthma exacerbation or another clinical allergy.

2. **Are the different causal relationships adequately structured? If no, please explain.**

- The presented diagram looks too much straightforward. I miss feedback loops and effect modifications.
  An example for the latter is the action of air humidity to protect against fine air bore particules that was observed recently. So far it is unclear whether this effect occurs due to a protection of the mucosa or due to a changed spectrum in particles size under more humid conditions.

- A feedback loop might be provided by infections. Infections (especially gastro-intestinal infections) can protect against allergy (so-called hygiene hypothesis). In contrast, respiratory infections are discussed as a disease to aggravate symptoms of allergy.

- Another issue still missing in the diagram is combinations of stressors. For example, it is known from earthworms that fluctuations in temperature 'harden' the worm against heat, i.e. make it more resistible (so-called heat hardening). A coexistent burden with chemical substances significantly decreases the worm's ability to 'heat harden' and, in this way, reduces its resistance. The demonstration of an analogous effect for human health is still open.

- Climate change may lead to increase of some allergenic plants but also to a decrease of other allergenic species.

- Improvement in building techniques will probably somewhat decrease the association between climate change and building dampness

- It is not clear the reason why the firs box contains the effect (Worsening) and the boxes below don't. For example the box "Respiratory morbidity Preterm mortality". If the decreased exposure to cold is taken into account (correctly), there should be a slight positive effect on respiratory diseases in term of a reduced susceptibility to upper respiratory infections and to the direct effect of cold air inhalation (broncho constriction). Then it would be more clear "decreased winter respiratory morbidity" or something like that. Moreover, "Sensitization to allergens" means Increased "Sensitization to allergens" or New allergens or both?

- The causal relationship is oversimplified. Air pollution assessment mentions only fine particulate matter PM2.5, which represents only one component of air pollution impact, representing mainly traffic related air pollution. Impact of climate change, is more complicated than represented in diagram, and may require more detailed (air pollutant specific or air pollution source specific) explanation.

- The magnitude is unclear, there should probably be a network of arrows with + and - on

- New, different types of weather could be implicated to asthma symptoms in certain areas. With milder winters children spend more time out of their houses, therefore exposed for longer time to various air pollutants.

PART B - EVALUATION OF THE INDIVIDUAL CAUSAL ELEMENTS

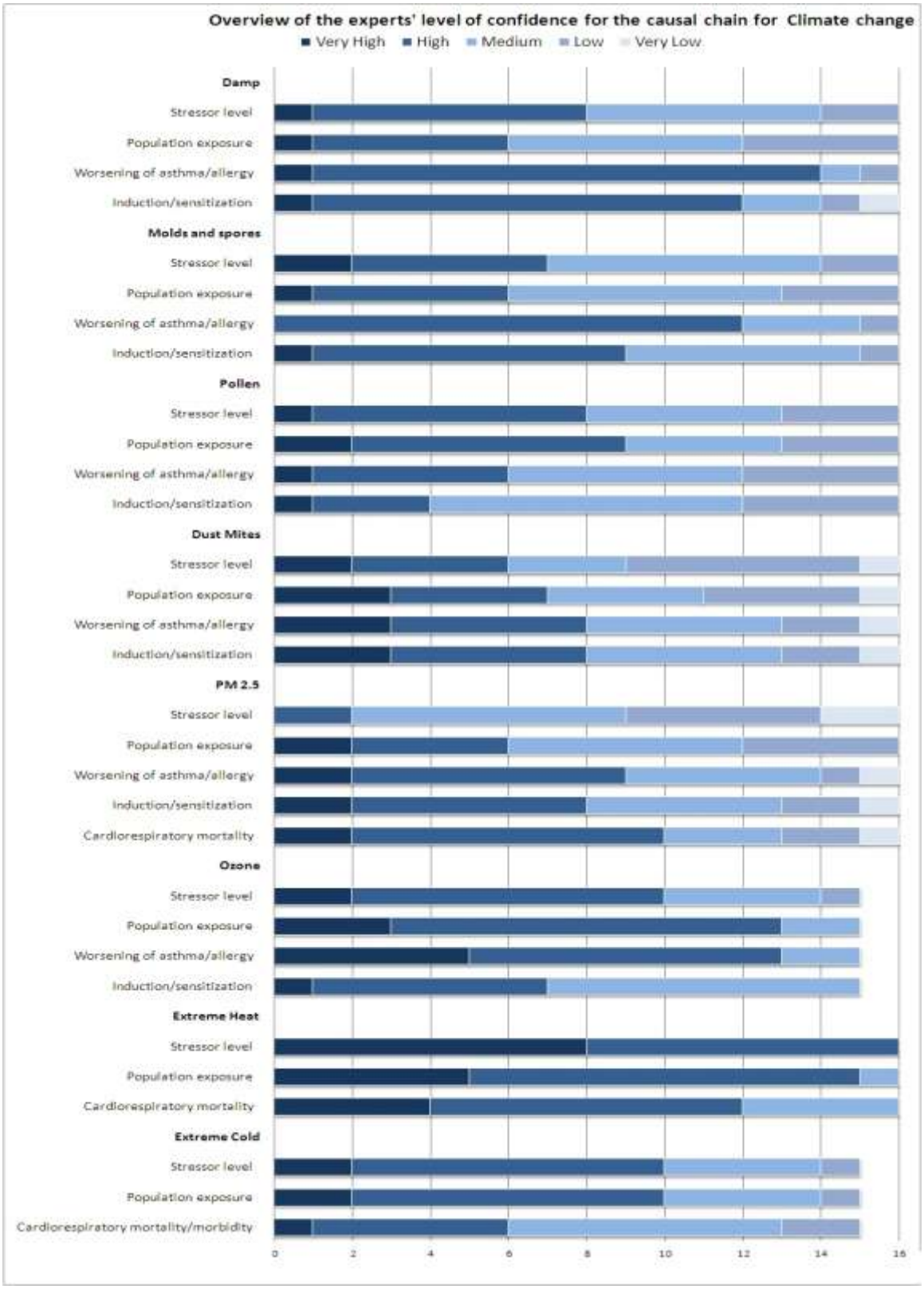


Figure 5: Results from the evaluation of the individual causal elements.

3. Cross cutting issues

Table 1: Relative importance of stressors

Stressor	Priority
Heat	3,25
Ozone	3,94
PM2,5	4,19
Damp	4,63
Pollen	4,69
Spores	4,88
Cold	5,38
Dust Mites	5,69

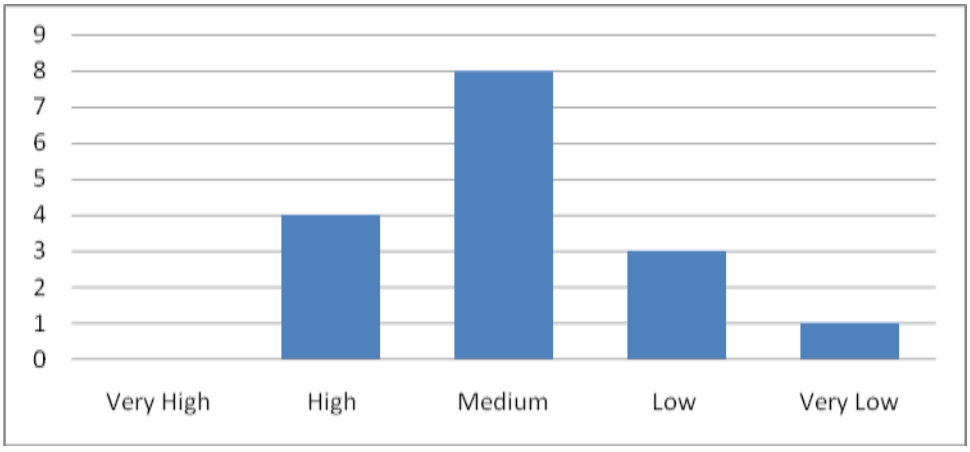


Figure 6: The level of confidence in the scientists' abilities to predict the magnitude of the overall impact of climate change on respiratory morbidity and mortality rates.

Final comments (14 experts):

- We need more data on particle size and composition in various parts of Europe, not only big cities. We need more experimental (laboratory) data on the interaction climate change - air pollutants.
  We need a widespread monitoring network of pollens, to be analyzed together with weather and pollution data.

  Any impression on the usefulness at this stage would be precipitous. It is better to wait for the results in order to understand whether the questions and especially, the scores were adequate.
- There is obviously a relationship between climate zone and level of exposure to moulds and bacteria and house dust mites in the population, but other factors such as diet, lifestyle, air pollution from traffic and industry modifies the relationships, so there is no clear relationship between asthma prevalence and climate zone.
- Moreover, there might be a genetic selection, with differences in susceptible genes for asthma and allergy in relation to climate zone. This makes predictions hard to perform. There is evidence of the highest increase of asthma in middle income countries; they are usually in a temperate or warm climate zone.

- The effect of climate change will probably be very different in different parts of the world, so the evaluation is unclear with respect to that, I have taken it as the general global trend, but we need to sort this things out for different parts of the world.

- The evaluation on the impact of climate change on cardio-respiratory mortality as in the last question is misleading. The rank should not include allergens, moulds and dust mites because this could be causes of an increase in respiratory morbidity but not cardio-respiratory mortality.

- As already stated above, I find this evaluation too much oversimplified. For example, there is always asked for changes in the LEVEL of a certain pollutant/stressor. My opinion is that the spectrum (chemical composition, size fractions,) will change and this has a very diverse impact to respiratory health: some changes worsen, but other changes can improve health.

  Nevertheless, important conditions for respiratory health are addressed in this evaluation.

- A causal diagram as shown and used in this evaluation can never catch all aspects and possibilities of interactions. With this in mind it is always important to establish a good monitoring on the environmental changes as well as on the clinical aspects. The causal diagram might then correspondingly be adopted.

- It not only depends on climate change and medical expertise. I cannot predict adaptation measures. e.g.: More rain does not necessarily mean more moldy homes. It also depends on technical measures and changes in building materials in reaction to a changing climate. So this evaluation helps to highlight necessary adaptation measures, but is not able to forecast "number of additional cases"!

  Ozone: I always thought it is more UV than heat that triggers the O3 formation. And when we have more rain we will have more clouds and less O3!?

  In my data PM2.5 is still a phenomenon of the cold season. So I am not so much concerned about heat related secondary particles yet.

- Some of the questions difficult to answer, because it depends on what outcome you are referring to - e.g. cardiovascular mortality is one thing and incidence of childhood allergy is something else, each with unique and common risk factors.

  Being a pediatrician with experience in research on environmental risk factors for asthma/allergy, my personal knowledge about climate change and its effects on the weather patterns incl. heat and cold episodes is unfortunately limited.

- The more scientific knowledge on how climatic changes will impact on respiratory morbidity and mortality we get, the better we could argue for climatic policy.

TRAFFIC: PART A - THE STRUCTURE AND COMPLETENESS OF THE CAUSE-EFFECT DIAGRAM

1. Does the diagram take into account all of the important parameters when evaluating the asthma and allergy risks related to traffic pollutants?

5 experts replied YES, and 4 replied NO. The suggestions by 4 out of 10 experts are:

- The parameter " time of exposure" is missing: It is pretty clear that throughout life exposure to air pollutants can trigger acute events and symptoms. But for the first initiation of the asthma disease and for the sensitization to certain airborne allergens the time-window of susceptibility is still poorly defined. Asthma is a poly-causal disease. Allergic asthma is only one part. It would make sense to study development of atopy and allergy independently from studying the outcome "asthma". Air pollution might trigger other forms of asthma as well.
- Add weight (BMI) to the predisposing factors.
- The middle box presumably is meant to reflect processes in men. The possibility that traffic related pollutants might alter allergen carriers (pollen) is neglected. The predisposing factors give only a small list of possible predisposing factors (exposure to farm-living, number if siblings, type of nutrition and so on) that should be indicated somehow. It is not necessarily air-way inflammation but there might be the possibility that oxidants penetrate impaired skin (eczema).
- Predisposing factors should include dietary factors related to antioxidant defense.

2. Are the different causal relationships adequately structured

7 experts replied YES, and 2 replied NO. The suggestions by 3 out of 10 experts are:

- There is an ongoing discussion regarding how to define asthma and if asthma should be defined as a disease (yes/no) or by some kind of score based on asthmatic symptoms. Suggests adapting to the score approach, adding another box in between the second and the third including different asthmatic symptoms.
- Predisposing factors might also act on the link between inflammation and asthma
- The figure could be made more complex

3. **Are there any unnecessary parameters shown in the diagram that could be deleted**

One expert replied YES, and 8 replied NO. The suggestions by 1 out of 10 experts are:

- Uncertain if it is known that airway inflammation induces sensitation.

CROSS CUTTING ISSUES

The diagram illustrates different proposed or potential ways through which traffic exposure could lead to induction of asthma and/or sensitisation. On a scale of 1 to 6, please rank the relative importance of each proposed or potential association in comparison with the health impact to be expected via other pathways.

Pathway	Relative importance
Wear particles : Induction of asthma	2,67
Wear particles: Induction of sensitisation	2,89
Primary exhaust components: Induction of sensitisation	3,11
Primary exhaust components: Induction of asthma	3,33
Secondary pollutants: Induction of asthma	3,56
Secondary pollutants: Induction of sensitisation	3,67

Please comment on any key areas of knowledge which you think are underdeveloped

- Best data base exists for primary exhaust particles and some of their chemical components followed by some secondary pollutants. There is little data on the impact of coarse particles on asthma. Could be due to mechanisms other than sensitization, though some chemicals in tires that could act as allergen or as adjuvant. Still more research needed there!
- Characterisation of PM (traffic related or otherwise) to examine what is driving adverse health effects that are seen in numerous studies.
- Interaction between traffic exhaust exposure and dietary factors, and interaction between indoor and outdoor exposure. Moreover, the role of the age of the traffic exhaust exposure for the health effects. Also the role of wear particles needs to further evaluated.
- Air pollution and Excercise Induced Bronchospasm

PART B- EVALUATION OF THE INDIVIDUAL CAUSAL ELEMENTS

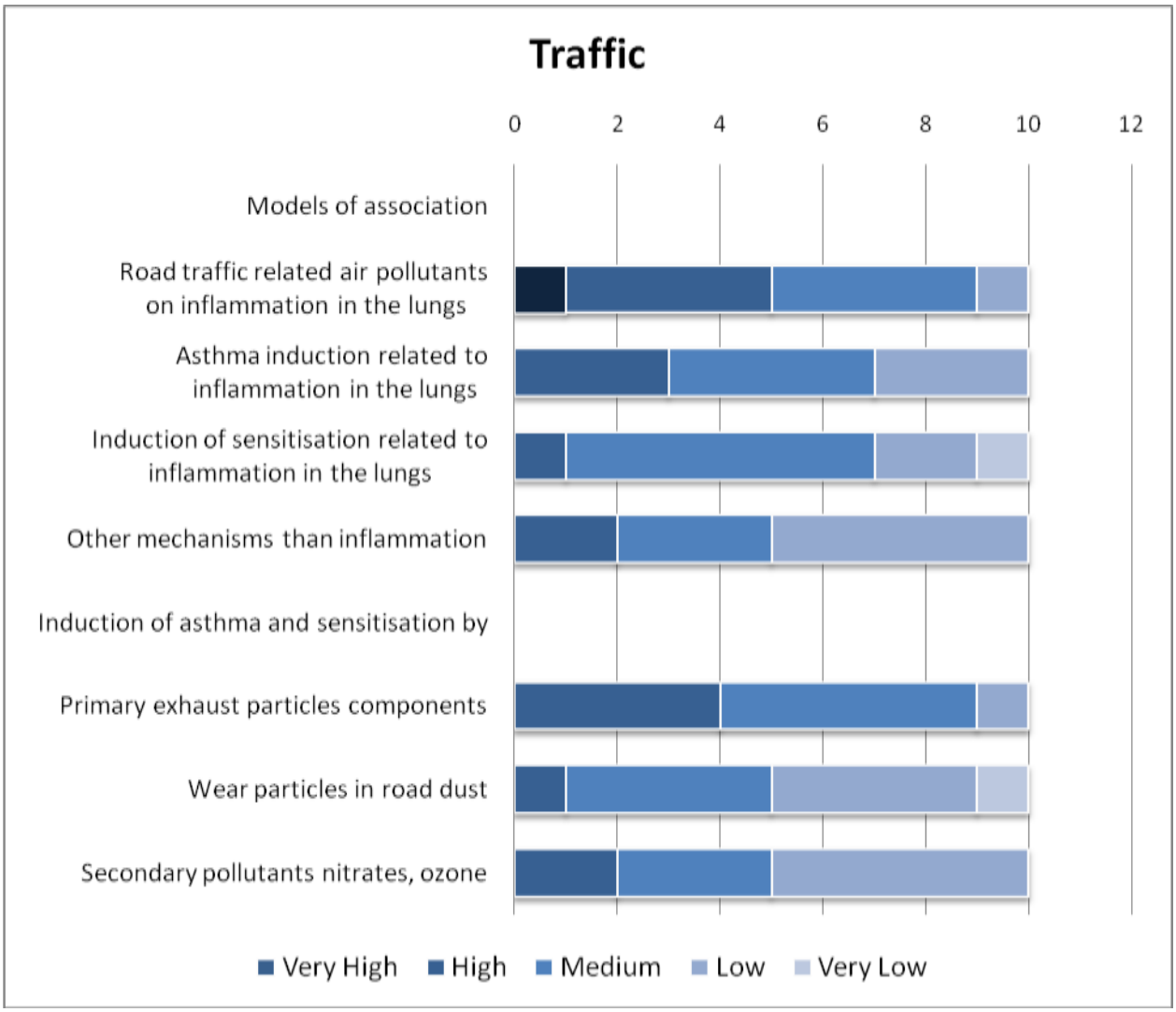


Figure 7: Results of the individual causal elements.

TOPIC 2: CANCER

The evaluation is still under progress.

TOPIC 3 NEURODEVELOPMENTAL DISORDERS

CHLORPYRIFO: PART A- EVALUATION OF THE INDIVIDUAL CAUSAL ELEMENTS.

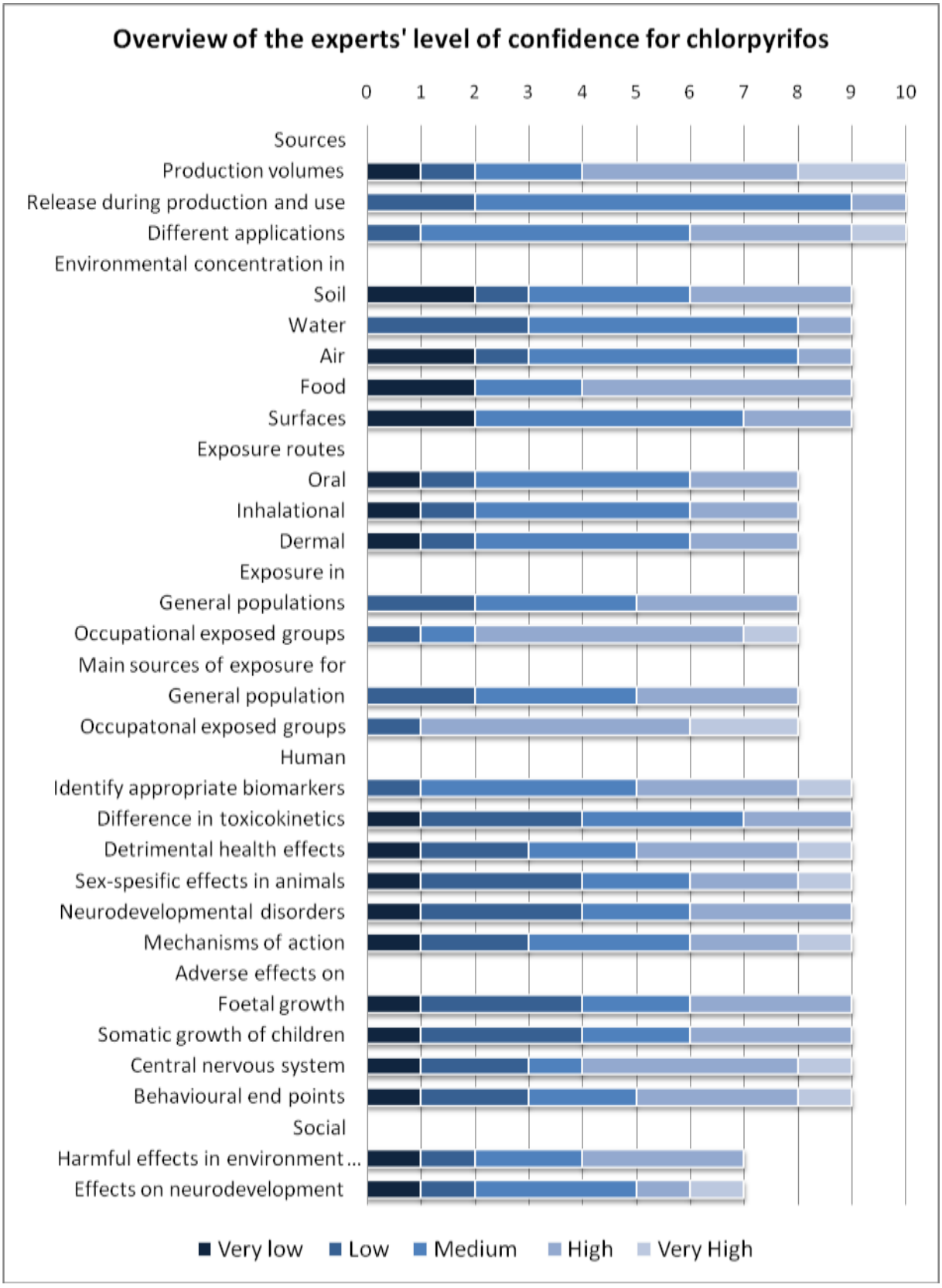
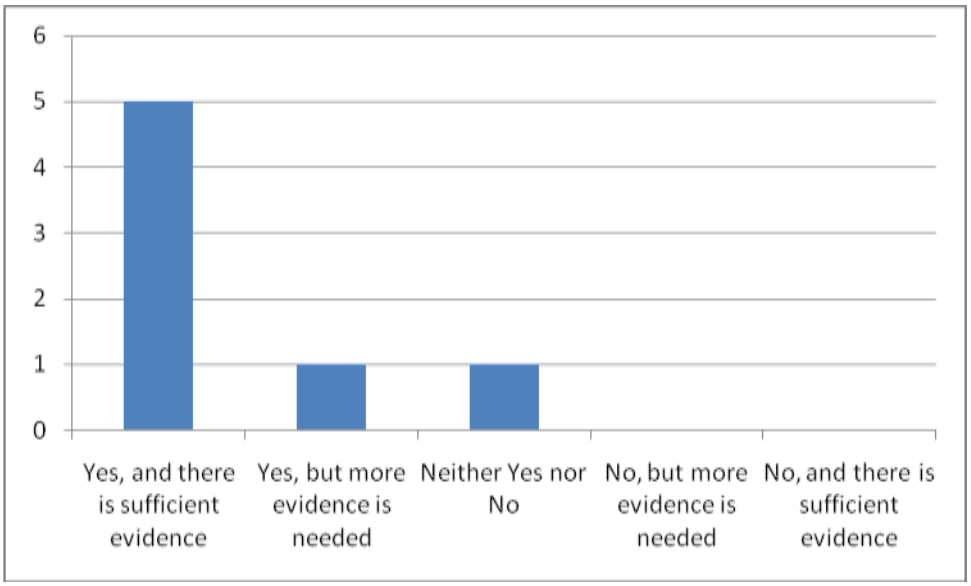
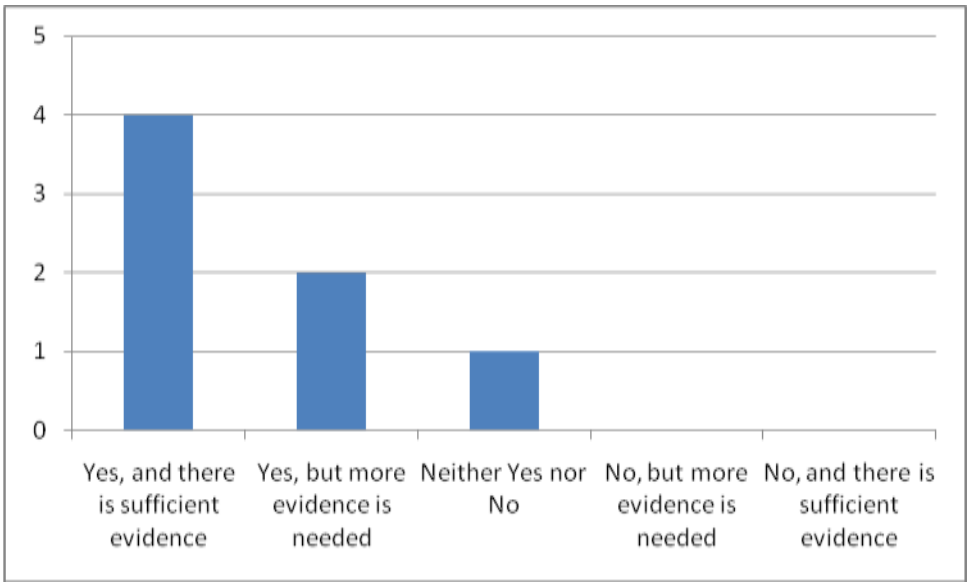


Figure 8: Results from the individual causal elements.

Should CPFs be banned from home use due to any factors?



Should CPFs be banned for home use due specifically to neuro developmental effects?



Do you feel there are other regulatory interventions justified by our current level of knowledge?

- CPF is fine for outdoor use, only concern is indoor use.
- Strict evaluation of current use in agricultural and domestic settings

Additional comments to the different part of the causal chain.

Sources:

- It is not specified whether the production volumes are global or not.
- Unclear about the meaning of different applications.
- It would be useful to provide information about the relative weight of CPF exposure in residential vs Agricultural use (just to give an idea of the contribution of the two sources)

Environmental matrix:

- Surfaces is a too generic term.
- What is meant by "predicting" concentrations? By modelling? Given the emissions of present sources?

Exposure:

- The term ambient is unclear. Could it be specified by adding (air, etc).
- The importance of dust is unknown: neither the sources that contribute to decaBDE in dust, nor the contribution of dust to the overall exposure, nor the main pathway (inhalation or ingestion of dust). This is especially the case for infants and children.
- What is meant by "predicting adverse effects"? Given a measured exposure? External or internal? Or starting all the way from the source?

Social:

- Strict evaluation of current use in agricultural and domestic setting.
- Question about the colours: The same colours through the different subdiagrams do suggest that there is a special link within the yellows (residential and indoor use, water, ambient), a special link within the oranges (agriculture and gardening, soil, occupational) etc.?

PART B- EVALUATION OF THE STRUCTURE AND COMPLETENESS

1. **Does the diagram take into account all of the important parameters when evaluating the risks related to production, use and discharge of Chlorpyrifos? If Yes, please explain.**

All the 7 experts replied YES.

2. **Are the different causal relationships adequately structured? If No, please explain.**

All experts except for one replied Yes. The one who replied No, found the use of colours misleading. I could not understand whether there is a yellow line, or a green line, etc.

3. **Are there any unnecessary parameters shown in the diagram that could be deleted? If Yes, please explain.**

All the experts except for one replied No.

TOPIC 4: ENDOCRINE DISCRUPTORS

BFR HBCD: PART A - EVALUATION OF THE STRUCTURE AND COMPLETENESS OF THE CAUSAL DIAGRAM 13 ANSWERS)

1. **Does the diagram take into account all of the important parameters when evaluating the risks related to production, use and discharge of HBCD?**

5 persons said YES, 8 persons said NO.

The different suggestions given by 6 of 13 persons were:

- More endpoints in health effects should have been included, not only general-, endocrine-, neuro-toxicology (3 persons). Eventually general toxicity could be followed by: a) characterization of critical effects identification b) dose response analysis (1 person).
- Food and biota are missing under environmental matrix (2 persons).
- A temporal component is missing under environmental matrix (1 person).
- Environmental matrix, does it cover possible human routes of exposure, for example dermal contact (1 person)?
- Scientific risk characterization with comparison of exposure levels and no adverse effect levels is missing (1 person).
- Uncertainty analysis of the scientific parameters is missing (1 person).

2. **Are the different causal relationships adequately structured?**

11 persons said YES, 2 persons said NO.

The different suggestions given by 3 of 13 persons were:

- Risk management, product stewardship and control of emissions are missing after assessing the risks (1 person).
- Place mode of action and NOAEL above the arrow. They are not health effects but they are important (1 person).
- Transport and transformation: add partitioning behavior between different compartments (e.g. Koa) and determination of main target compartments (1 person)
- Toxicokinetics: Add concentration-time relationship, AUC, absorption and elimination kinetics (1 person).
- Toxicology: Add reference to dose response analysis and identification process for critical endpoints (1 person).

3. **Are there any unnecessary parameters shown in the diagram that could be deleted?**

11 persons said YES, 2 persons said NO.

The different suggestions given by 3 of 13 persons were:

- How can political settings be taken into consideration when addressing risks of chemicals? This should be based on science (1 person)
- What is the meaning of optimal scenario, is it political action (1 person)?

- Water matrix is not relevant for hydrophobic contaminant (1 person).

PART B – EVALUATION OF THE INDIVIDUAL CAUSAL ELEMENTS

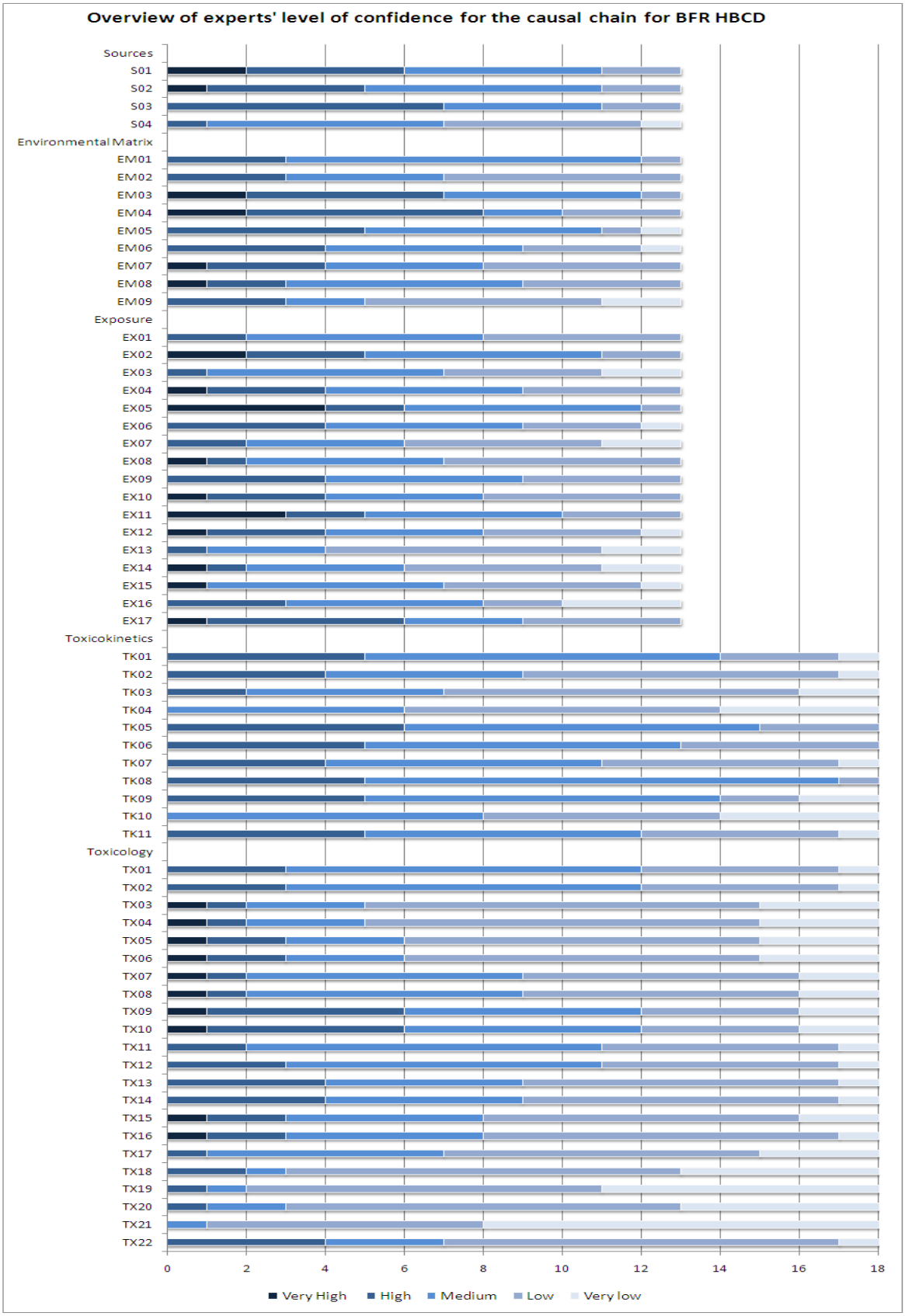


Figure 9: Results from the evaluation of the individual causal elements.

Final comments (18 answers)

Finally do you think that any relevant questions were left out or that any questions were superfluous?

The different final comments given by 10 out of 18 persons were:

- HBCD measurements in the past using GC/MS are questionable, compared to the LC/MS used today, since: the GC/MS measurements are not isomer specific, they are not using isotopically labeled IS and they are enabling isomerisation and/or degradation during the course of the analysis (2 persons).
- Different behavior of each HBCD diastereoisomer has been observed. The next phase in HBCD risk assessment should be to distinguish between the different enantiomers (2 persons).
- Effects on energy metabolism depending on an influence on leptin metabolism should be mentioned (1 person).
- Direct danger to vitamin K metabolism in utero based on induction of enzymes involved in degradation of vitamin K should be mentioned. Endpoint for toxicity assessment should therefore be induction of enzymes and not increase in liver weight (1 person).
- HBCD is now on the candidate list of REACH and already banned in Sweden (1 person).
- Interaction between different types of environmental pollutants or chemicals should be assessed (1 person).
- Information on the carcogenicity of HBCD is missing (1 person).
- Questions are difficult to respond since they are open to interpretation (1 person).
- It might be quite difficult and open to expert judgement to define the critical study to be able to predict NOAEL (1 person).
- Exposure: The importance, the sources, the overall contribution or the main pathway of exposure (inhalation or ingestion) of dust is unknown (1 person).
- Exposure of infants and children does not consider ingestion of dust (1 person).
- Environmental matrix: What does predicting concentrations mean? By modeling? Emissions or actual sources? (1 person).
- Toxicology: What is meant by predicting adverse effects? (1 person).
- Assuming the bioavailability to be 100% from ingestion is unlikely (1 person).
- The background paper does not include all data available on HBCD in dust and air and evaluation of significance of dust and diet as exposure routes (1 person).
- The background paper does not cover the large amount of different information available for HBCD. It was rather selective (1 person).
- The background paper contains some contradictions and indistinctness (1 person).

PHTHALATES PART A – EVALUATION OF THE STRUCTURE AND COMPLETENESS OF THE DIAGRAM

1. **Does the diagram take into account all of the important parameters when evaluating the asthma and allergy risks related to traffic pollutants? If no, please explain.**

8 experts replied yes, and 8 replied no. The experts had the following comments:

- Differential effects of exposure during different stages of development or life is not illustrated Potential transgenerational effects not taken into consideration
- The diagram suggests that food and infant exposure come about from envirnomental compartmnts of sediment soil water and air. But food can become contaminanted directly by packaging and mothers/milk can become contaminanted from cosmetica.
- Food intake and by skin contact (e.g. from toys and cosmetics) are missing. Behavour is important in exposure assessment.
- In the sources, unintended release during the production of phthalates is missing. Would also add developmental toxicology (with human body) and instead of reproductive toxicology with endocrine disruption.
- A number of factors between Dose and Health effects are not adequately addressed: biochemical or biological effects that are possibly related to a later disease outcome. This is not reflected in health effects/mode of action. Issues are gene expression, hormone induction/reduction.
- Part A “Environmental matrix”: Ground water, Surface water, waste water sludge and rainwater are not highly relevant for human exposure. Propose to delete these terms and include others like e.g. drinking water, food. The title "Environmental matrix" is also somewhat misleading. The concentrations in food for example are relevant informations too. The graph showing the “Exposure” is also unclear. On one hand the terms "Dermal" and "Inhalation" were used, on the other hand "Infant exposure" or "Food/water". This seems not very systematically. Also suggest the following terms "Dermal, inhalation, ingestion, Medical devices". In the graph "Human Body (left list)" the word "Metabolism" is missing.
- Diagram is fine in an overall and schematic way; missing information when it comes to details, e.g with regard to sensitive groups, differences in sensitivity due to life-stage at exposure.

2. **Are the different causal relationships adequately structured? If no, please explain.**

9 experts replied Yes, while 7 replied no. **The experts had the following comments:**

- The diagram is too linear.
- The last groups of topics are outside the scope on cause-effect relationships, but are important in relation to risk management.
- This is a fairly comprehensive figure and the following comments may be "nit-picking" or inappropriate. 1. Not clear why medical device is not included in "sources" 2. The diagram does not take account of interactions with other EDCs - this is crucial for understanding of NOALs.
- Food stuff probably is the major source of phthalate exposure of the general population. However in this diagram, one has to believe that concentrations in the environmental matrices are the source of phthalates on foodstuff. This is definitely misleading. How do get phthalates into foodstuff? Probably during processing, and contact with phthalate containing materials, PVC gloves in contact with foodstuff and so on.

- Should add mixture effects.
- Did not understand the indication of the causal relationship.

3. **Are there any unnecessary parameters shown in the diagram that could be deleted? If Yes, please explain.**

4 experts replied yes, while 12 replied no. The experts had the following comments:

- NOAEL is a very specific and technical term in a diagram that has to 'speak' to multiple disciplines
- The impacts part should be improved and linked somehow to an extended conceptual frame, see above. Unclear as to "optimal scenario" is.
- Mothers milk is a subdivision of infant exposure/food/water

Part B – Evaluation of the individual causal elements

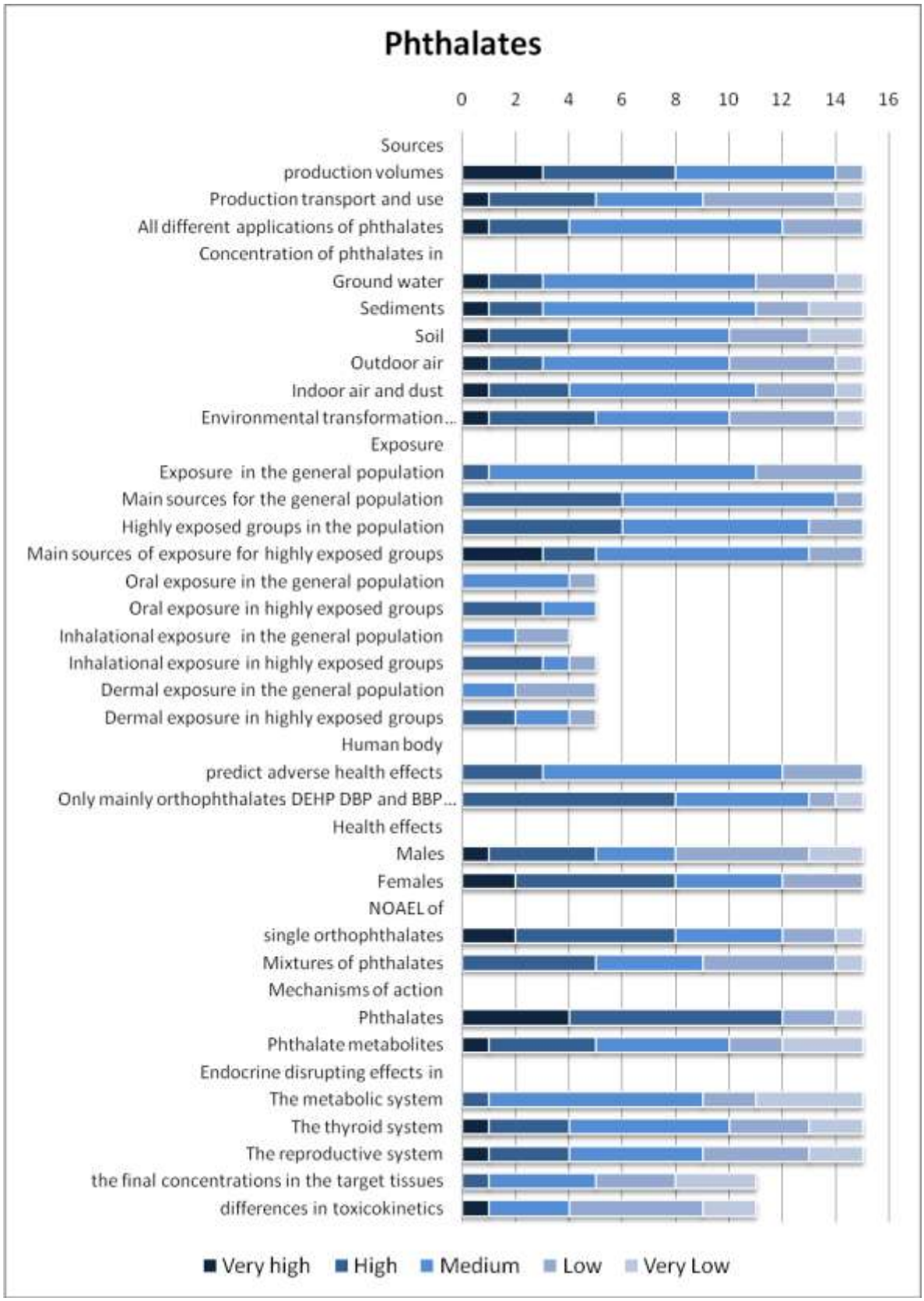


Figure 10: Results from the individual evaluation of the causal elements.

ANNEX 3: ALL AVAILABLE WORKSHOP REPORTS

TOPIC 1: ASTMA AND ALLERGIES

The workshop report is currently not available

TOPIC 2: CANCER

The workshop reports is not available

TOPIC 3: NEURODEVELOPMENTAL DISORDERS -WORKSHOP REPORT FOR CHLORPYRIFOS

BACKGROUND AND CONTEXT

- Organophosphate compounds, or OPs, are used worldwide in agriculture and gardening to control insects. They are commonly found in industrial products such as Dursban and Lorsban. They are also used indoors, especially for controlling cockroaches and termites. OPs act by inhibiting *acetylcholinesterase* (AChE), which affects nerve function in insects, humans and other animals. Most of the animal and human studies recently published refer to the OP *chlorpyrifos* (CPF).

- OPs are used in Europe for pest control. In 2003 they accounted for over 59% (4645 tonnes) of insecticide sales in the EU, with CPF the top selling insecticide (15.6%, 1226 tonnes). CPF was also used in the US for pest control, but the US Environmental Protection Agency (EPA) imposed a ban on the sale of CPF for home use in December 2001.

- There are concerns about the safety of CPF, especially in indoor settings. While previous studies have shown levels of CPF that are safe in adults, recent animal and epidemiology studies show the young may be more sensitive to CPF toxicity. CPF is a neurotoxin that affects synaptic transmission in neurons, which can lead to developmental and behavioural problems. This has led to concerns that it may affect children on a large scale and may be a contributing factor related to the large scale of emotional and behavioural diagnoses in Europe.

- CPF inhibits acetylcholinesterase (AChE), leading to excess transmitter molecules in the nerve synapses. These then cause persistent overstimulation of the receptors and lead to functional changes in tissues and organs. CPF is an EPA class II toxicant (oral dose LD50 is 50-500mg/kg). CPF may also act by other mechanisms: low, nontoxic doses affect neural cell development. Animal studies show CPF targets neural systems further, affecting norepinephrine, dopamine, and serotonin. Glial cells are sensitive to CPF. This can lead to hyperactivity, learning impairment and emotional effects in rats. Animal studies show the young are more susceptible to OP toxicity than adults. Low-dose exposure produces neurochemical changes even at doses below traditional toxicity. Differences in young animals are caused by incomplete metabolism and the susceptibility of the developing nervous system.

- Exposure during pregnancy can lead to premature birth and reduced length and birth weight in infants. Follow-up shows abnormalities at the age of 3, as would be expected with prenatal growth retardation. Such effects, combined with those of other neurotoxic industrial chemicals, could lead to a 'silent pandemic' of pervasive, nonspecific developmental disorders that might affect a large proportion of the population.

Expert Elicitation

An expert questionnaire was administered in order to evaluate the state of the current scientific knowledge and highlight important policy considerations.

- In light of current, albeit limited, knowledge available on the risks of CPF, most experts are in favour of a precautionary ban or restrictions on its use.

- Most experts agree that more research and monitoring is needed in order to develop a better understanding of the risks involved in the use of decaBDE.

- Experts agree that the three priority areas to investigate are:

1. *Population behaviour*, including occupation, diet, and at-home use,
2. *Physical processes*, such as uptake or absorption, since these determine exposure, and
3. *Pathophysiological processes*, like enzyme function, which determine exposure outcome

Preventing potential adverse effects on human health caused by CPF is a task for authorities around the world. Taking appropriate political actions requires sufficient knowledge on the outcome of indoor exposure. The required weight of knowledge that is needed to support policy measures is open for debate amongst experts, policymakers and stakeholders. Monitoring, modelling, epidemiological and experimental research are quite resource intensive with regards to time and money. Therefore, the most important issues must be identified and prioritized.

To identify knowledge gaps and potential agreement or disagreement on the different aspects of the CPF issue a causal diagram illustrating scientists' current understanding of the cause-effect relationship between the production and use of CPF and its potential impact on health was made. The diagram was based on the latest review articles and reports available. A group of experts was asked to express their confidence in the current knowledge in the different parts of the diagram by completing an online questionnaire. From these experts a group of eight was selected to complete a second questionnaire and take part in an expert panel workshop where the implications of the results of the two different evaluations for policy and health were discussed. Priorities for further action were identified and the workshop aimed at arriving at a final expert advice for policy makers.

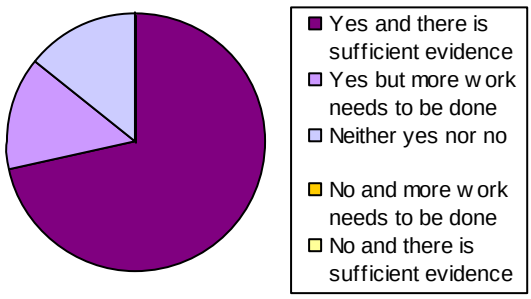
A large number of animal and epidemiology studies suggest a risk of developmental disorders in children, even at levels of exposure to CPF that would be safe in adults. This could contribute to learning disorders, ADHD, and motor impairment. Before birth, this damage may be due to the vulnerability of

the developing nervous system. After birth, they may be due to the different ways in which children interact with their surroundings.

While the case for specific neurotoxicity of CPF is still an area of intense research, studies seem to point to effects in infants and children that could be as serious and as pervasive as those of known neurotoxicants such as lead and mercury.

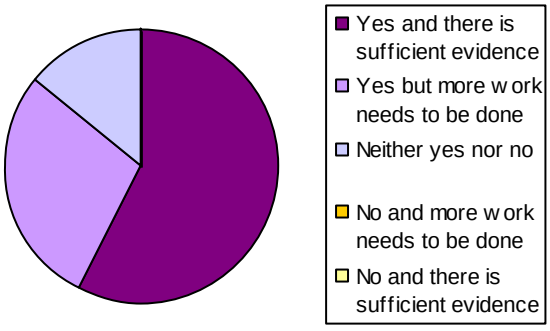
A ban on residential use of CPF has been in effect in the US since 2001 but the EU has no such restrictions. A number of scientific experts were consulted about the evidence for a ban on CPF within the EU. They were drawn from the research community and have all published studies on the subject.

They gave their opinions regarding the quality of evidence for a clear risk, results of which varied across the spectrum from *very high* confidence in the evidence to *very low*. Many felt more research was necessary to quantify the risk involved. However, when asked *whether CPF should be banned from home use*, the majority agreed.



As the graph shows, none of the experts chose the 'No, and more work needs to be done' or 'No, and there is sufficient evidence' options.

When asked if CPF should be banned due to *specific neurodevelopmental effects*, again the majority agreed.



When asked what has the greatest effect on health risks from CPF, these areas were identified:

- *Population behaviour*, including occupation, diet, and at-home use,
- *Physical processes*, such as uptake or absorption, since these determine exposure, and
- *Pathophysiological processes*, like enzyme function, which determine exposure outcome

Pre- and post-natal exposures were considered important. Specific questioning for more detail revealed:

- 'Frequency and duration of exposure… affects health risks'
- 'Age and genetic polymorphisms influence toxicity'
- 'More research needed… in low doses of chlorpyrifos.'

There was high confidence that research can decisively contribute to reducing problems, and even more in the potential for policy action to do so. One scientist commented changes in policy were 'feasible immediately'. More data about exposure, better scientific understanding, and CPF monitoring were widely supported.

Further comments included 'I think CPF is fine for outdoor use…indoor use is of concern.' Another suggested 'strict evaluation of current use in agricultural and domestic settings.' There appears to be a large amount of evidence indicating neurotoxicity of CPF, and substantial scientific support for an EU domestic use ban.

An expert consultation was held following the results for the first questionnaire and a second, more detailed one.

- Results seemed to indicate much variation in the confidence of the effects policy making might have in the next 5 years. Discussion then focussed on the reviews of the available literature and a discussion of whether the scientific evidence was sufficient to support a ban, possible problems with widely-cited studies, and the question of whether it was possible to know to what extent indoor exposure is a problem in the EU.

- It was generally agreed that the data regarding home use in the EU is thin, if not nonexistent. Questions were raised as to what extent the large volume of CPF sold in the EU is used in non-agricultural applications, and if so, what is the delivery method (spot-spraying vs. 'bombs', for instance).

- It was also agreed that more information is needed regarding the process behind the 2003 and 2008 EU statements regarding he continued allowance of CPF for indoor use.

- It was agreed hat topics to follow up include both of the above, as well as body burden. Also the design of future in vitro and animal studies should be improved to see whether the effects are indeed occurring at concentrations below those that would induce cholinesterase inhibition - is this the main route of action for the purported neurodevelopmental effects, or is there some other action at work? Also considering whether it is possible that CPF itself is not the problem but is a proxy for some other substance, combination of substances, or confounding factor.

- Further discussion between the experts agreed on ways to improve the reports currently being prepared in the HENVINET project, but also that even after discussion the answers given regarding recommendations would remain unchanged. However there is much scope to improve the basic knowledge behind the reports, no just to include in vitro and in vivo studies and epidemiology, but also usage studies and some human geography

considerations. In doing so we may come up with a more targeted review that would be more generally acceptable across the diversity of opinion.

- The anticipated output from this effort, apart from internal project documentation, may include a methodological paper, a comment or letter to a scientific journal, and further posters and presentations at conferences.

- Several food for thought points were put forward for further consideration:

1. When do 'we' know enough for what and who decides? What is 'our' main ambition?
2. Which criteria are important for deciding on the meaning & weight of knowledge?
3. Which criteria for deciding on the relevant body of knowledge?
4. Which criteria for the 'right' (group of) experts?
5. Where does science become personal interpretation? From (lack of) data & uncertainties to science to knowledge from a problem solving perspective
6. The proof of science is in the discussion?

POLICY OPTIONS

The prior consideration and rejection of a indoor use ban for CPF twice before, in 2002 and 2008, raises the question of what impact current knowledge assessment may have on future policy options.

More data and better understanding were indicated by the experts as being tasks for science to address in the next five years. Funding for fundamental science which focussed on population behaviour and physical processes was particularly emphasised. For applied science, developing interventions in these areas was favoured.

Concrete action by policymakers turned up a wider range of views. At its most basic level, EU-level monitoring of population behaviour, physical processes, dispersion and transfer, and other actions was supported. Awareness raising in terms of possible risks due to population behaviour was also indicated, with one expert feeling strongly that there is enough information as we have it to enact prohibitory policy straight away with an eye towards altering usage of the products in homes, with a ban on home use considered to have the most direct effect on outcomes. Once this was in place it was then suggested that science and policy might then turn to the question of whether agricultural applications were also safe.

Confidence that these suggestions could be achieved in the scientific realm over the next five years were *medium* and *high*. Confidence that policy could achieve these in the next five years ranged more widely from *low* to *very high*.

SUMMARY

Areas of concern: Population behaviour and physical processes were two areas considered to be the most important determinants of toxicological outcome by the expert group.

The arguments: There is limited data on mechanisms of effect at low, sub-toxic levels but also a request for more epidemiological evaluation of the risk issue. More focus in the future should be addressed on design of studies being appropriate to relistic exposures in the home that are suitable to the EU.

Type of action: Experts suggested more scientific research with focus on more data and better understanding of fundamental science. Also a request for policy action, especially more monitoring activities, but also some restricting and prohibiting activities.

Form of action: Concerning toxicology, was to determine whether factors influencing the use and prevalence of CPF in North America were also applicable here, and to examine whether exposure at a sub-clinical level has a measurable effect.. With regard to policy action there are some ideas about decreasing or stopping this exposure by restricting certain activities. Examination of whether CPF is due to be re-examined for restrictions, as such restrictions have been rejected in the EU twice before, were discussed. More knowledge of why bans were not considered appropriate was deemed necessary.

Confidence in science: Most people in the group have some confidence in science coming up with usable or decisive knowledge within the next five years

Confidence in policy action: As indoor usage resitrictions for CPF have been considered and rejected in the EU before, there were questions of whether policy makers could be motivated to examine the area further, although preventative action and its relationship to the precautionary principle were discussed.

TOPIC 4: ENDOCRINE DISRUPTORS - WORKSHOP REPORT FOR HBCD

KEY MESSAGES

Policy context

- HBCD is one of the major brominated flame retardants (BFRs) used today. BFRs are applied to prevent electronics, clothes and furniture from catching fire. The commercial formulation of HBCD contains three stereo-isomers: □-HBCD, □-HBCD and □-HBCD.

- A sharp increase of the HBCD concentrations in the environment has been detected by several investigators since 2001, probably caused by the increased use of HBCD when other BFRs were banned or withdrawed (penta- and octabrominated diphenyl ether (PBDE) mixtures (Penta BDE, OctaBDE).

- The major concerns about HBCD are its persistence and its potential for bioaccumulation. The compound is found in high concentrations in both animals and nature.

- There are indications of toxicological effects of HBCD, especially in the liver and thyroid gland. Also, once in the body, HBCD is able to be metabolized and transformed into isomers of HBCD that are more bioaccumulative than the technical mixture of commercial HBCD.

- On June 2nd 2009 the European Chemicals Agency (ECHA) within the REACH framework decided to restrict the use of HBCD within the EU such that it only can be used when "authorized" for specific purposes. HBCD is also currently proposed to be reviewed for a global agreement of restriction by the Stockholm Convention.

- Alternative substances to HBCD with putative lower risk have been proposed, such as: halogenated flame retardants in conjunction with antimony trioxide, organic aryl phosphorous compounds, chlorinated paraffins, decabromodiphenylether, and ammonium polyphosphates, Potential risks of these compounds are limited and further investigation is required.

Policy options

An expert workshop was conducted in order to evaluate the state of the current scientific knowledge and highlight important policy considerations.

- Experts agree that more information is needed about the HBCD compound in order to better understand its health impact. This requires more investment in fundamental science as well as certain policy measures such as monitoring activities.

Experts agree to three priority areas for further investigation:

1. More knowledge, especially in humans, on the behavior of HBCD in the body, the mechanisms of action of HBCD and how HBCD affects health and illness of populations (toxicology and epidemiology).
2. More knowledge on the concentration levels of HBCD in the target organ (absorption, distribution, metabolism and excretion of HBCD).
3. More knowledge on the extent of exposure to HBCD; especially human exposure and exposure to the general population.

Furthermore the following issues are proposed for better understanding:

1. The different behavior of the different HBCD stereo-isomers must also be addressed.
2. Effort should also be invested into research on the toxicity and environmental behaviour of the most frequently proposed alternatives to HBCD.
3. In order to accelerate the rate at which policy relevant information becomes available, experts feel that research collaborations between publically funded institutions should be organised at the European level.
4. In addition to publically funded research, industry should be required to provide more toxicological data.
5. Policy makers must take decisions and invest more money in the required research.

- Based on the answers from the questionnaire and discussion at the workshop, the invited experts were not in agreement on whether or not the knowledge currently available is sufficient to justify more strict policy actions at this point. While some experts feel that the persistence and bioaccumulation properties of HBCD are enough to justify a ban or restrictions on use, others feel that more data is required before a decision to change the status quo is justified.

- Experts disagree as to whether, given five years and adequate resources, additional research would yield decisive knowledge on the key issues related to HBCD and its alternatives. Experts have a medium to high degree of confidence in the possibility that policy actions to effectively manage the health risks of HBCD to be either technically (not necessarily politically) feasible now, or will become so within the next five years.

EXECUTIVE SUMMARY

Situation

Brominated flame retardants (BFRs) are the major group of chemical flame retardants consisting of bromine containing organic compounds. BFRs are applied to prevent electronics, clothes and furniture from catching fire. Hexabromocyclododecane (HBCD or HBCDD) is one of the major BFRs. HBCD has 16 possible stereo-isomers with different biological activities, therefore the substance poses difficult problems for manufacturing, production and regulation (European Commission). The technical mixture/commercial formulation of HBCD contains three isomers: 75-89% □-HBCD, 10-13% □-HBCD and 1-12% □-HBCD.

HBCD is used in construction and insulation boards, packaging material, electrical and electronic equipment, upholstered fabric and textiles, bed mattress, furniture, seatings, draperies, wall coverings, indoor textiles and automobile indoor textiles (European Commission). At present, according to BSEF, the brominated flame retardant industry panel, HBCD is the only suitable flame retardant for some of these applications.

The global production of HBCD was 16700 tons per year in 2001 and 23000 tons per year in 2008 (BSEF). This correlates well with a sharp increase in HBCD in the environment detected by several investigators from 2001 onward (Law et al.), and is most probably caused by the increased use of HBCD when other BFRs were banned or withdrawed (penta- and octabrominated diphenyl ether (PBDE) mixtures (Penta BDE, OctaBDE). In Europe today there is only one production site today, in the Netherlands.

HBCD's toxicity and harm to the environment is currently being discussed. The EU Risk Assessment (RA) of HBCD for environmental and human health was initiated in 1996 and finalized in 2008 (BSEF). The RA concluded that no risk to consumers was identified, and no risk for workers was identified when standard hygiene measures are applied. Further the RA concluded that HBCD has persistent, bioaccumulative and toxic (PBT) properties due to the reported increased environmental concentrations, the concerns linked to these higher concentrations, and the several specific risks identified in the aquatic environment. In june 2008 HBCD entered a screening procedure under the new legislation REACH (REACH). On June 2nd 2009 the European Chemicals Agency (ECHA) within the REACH

framework decided to restrict the use of HBCD within the EU such that it only can be used when "authorized" for specific purposes (ECHA). In Japan under the Chemical Substances Control Law (CSCL), HBCD was classified as a Type 1 Monitoring Chemical Substance since April 2004. The US Environmental Protection Agency (EPA) will finalize a review of HBCD in 2012. Canada will publish a risk assessment of HBCD during 2009. Furthermore, HBCD is currently proposed to be reviewed under the global framework of the Stockholm Convention on Persistent Organic Pollutants (POPs) (Stockholm Convention on Persistant Organic Pollutants (POPs)). HBCD is also included in the list of substances added to a proposal to revise the RoHS (Restriction of Hazardous Substances) directive (RoHS Directive).

Alternative substances to HBCD with putative lower risk have been proposed (ECHA_2), but needs further investigation.

Background

HBCD is a ubiquitous contaminant in the environment, wildlife and humans due to widespread use, low volatility and low water solubility (Covaci et al.). HBCD can be found in environmental samples such as birds, mammals, fish and other aquatic organisms as well as soil and sediment, but also in the anthroposphere. Humans can be exposed to HBCD by inhalation of vapor and airborne dust through ingestion and by dermal contact, babies can be exposed during pregnancy and breast feeding, workers and consumers are mainly exposed through inhalation and dermal routes and exposure in the environment occurs mainly via the oral route (European Commission). HBCD is easily taken up and stored by organisms, especially in adipose tissue. Animal studies have shown that a technical mixture of HBCD is transformed in the body to an HBCD isomer that is accumulated to a greater extent in the body (Chengelis C.P.;Covaci et al.;European Commission;Zegers et al.). Also in nature a similar transformation occurs mainly via microorganisms (Davis et al.;Davis et al.;Gerecke et al.). Animal studies have confirmed a low acute toxicity, but liver weights were increased, liver enzymes were induced, and thyroid hormone levels were affected (Canton et al.;European Commission;Germer et al.;van, V et al.;van, V et al.). We do not know anything about similar effects in humans. One recent Dutch study on human prenatal exposure to HBCD and other organohalogans show effects on sexual and psychomotor development in healthy infants (Meijer et al.).

To identify knowledge gaps and potential agreement or disagreement on the different aspects of the HBCD issue a causal diagram illustrating scientists' current understanding of the cause-effect relationship between the production and use of HBCD and its potential impact on health was made. The diagram was based on the latest review articles and reports available.

A group of experts was asked to express their confidence in the current knowledge in the different parts of the diagram by completing an online questionnaire. From these experts a group of eight was selected to complete a second questionnaire and take part in an expert panel workshop where the implications of the results of the two different evaluations for policy and health were discussed. Priorities for further action were identified and the workshop aimed at arriving at concrete expert advice for policy makers

Assessment

Our first step in developing an expert advice on HBCD for policy makers was focused on prioritizing the results from our expert consultation: how severe are specific results with regard to public health risks? The results were used to set priorities of further attention for policy uptake.

The priority knowledge gaps

The top area issues that the expert panel group considered to be the most influential for the health impact for HBCD was *toxicology* and *concentration in the target organ and exposure. Toxicology* concerns the effects of a substance inside the body, and this area issue was ranked as number one. A request for more toxicological and epidemiological evaluation of the risk issue was raised. *Concentration in the target organ* is a result of exposure and toxicokinetics, (more specifically what happens to the substance inside the body, how the substance is absorbed, distributed, metabolized and excreted). Toxicokinetics was ranked as number two. *Exposure* deals with the different routes of exposure, e.g. inhalation, ingestion, dermal.

Most experts in the panel had medium to very high *confidence in science* coming up with usable or decisive knowledge within the next five years if given sufficient resources. Most experts moreover had medium to high *confidence in* the possibility that *policy actions* to effectively manage the health risks of HBCD will become technically (not politically) feasible within the next five years.

Weight of knowledge

During the expert panel discussions there was a general opinion that it is very difficult to be very certain about HBCD since there are less data available for this compound than for e.g. decaBDE. More specifically, there is a lack of epidemiological and toxicological studies, especially in humans (European Commission). There are limited data from toxicological studies of the targets of HBCD and of the mechanisms of action of HBCD. In addition there is very little information of the concentrations of HBCD in the target organs, first of all due to lack of adequate studies on absorption, distribution, metabolism and excretion, but also because HBCD is metabolized to other HBCD isomers in the body that are behaving differently from the technical mixture (European Commission;Zegers et al.;Hamers et al.;Palace et al.). It was also argued that there is a data gap on human exposure to HBCD, too little is known about normal exposure to the general population. Some exposure studies on children exist on sexual and psychomotor development in healthy infants (Meijer et al.) and estimations of exposure of occupational workers have been done (European Commission). Also the expert panel group considered that HBCD measurements performed in the past using the GC/MS technique are questionable compared to the LC/MS method used today (Abdallah et al.;Law et al.).

Experts *disagreed* on the extent to which knowledge on the risks of HBCD justifies a more drastic policy intervention. On the basis of the persistence and bioaccumulation properties of HBCD, most experts suggested that policy makers should introduce regulations on restricting and prohibiting activities. Other experts felt that more data and better understanding are required before such drastic policy

measures can be justified, they also claim that the use of suggested alternative compounds (ECHA_2) is not proven to be safer, and developing safe alternatives take time. One expert considered restrictions and prohibitions of the compound ethically justified, stating that it is not morally just to risk polluting a whole population in order to prevent a couple of fires. The same expert also pointed out that studies performed on certain BFR-like compounds (TCDD, HxCB, DDT, and PCB) constitute a sufficient basis to justify, by analogy, concerns about the health effects of HBCD to humans (Bouwman et al.;Bouwman et al.;Pelletier et al.;Tremblay and Chaput;Pacyniak et al.). Other experts strongly disagree to this since they do not consider TCDD or HxCB to be BFR-like. Also they point out that HxCB has never received a dioxin TEF-value, no BFRs are considered dioxin-like in terms of being given a dioxin TEF-value.

It was suggested that in order to achieve what we want more investment in fundamental science as well as policy measures such as monitoring activities is required.

It was claimed that there is no laboratory or institution in Europe where politicians and officers can initiate such studies such as those within the US NTP program.

Based on the answers from the questionnaire and discussion at the workshop, the invited experts were not in agreement on whether or not the knowledge currently available is sufficient to justify more strict policy actions at this point. While most experts felt that the persistence and bioaccumulation properties of HBCD are enough to justify a ban or restrictions on use, others felt that more data is required before a decision to change the status quo is justified.

RECOMMENDATIONS

- **More research data and monitoring on HBCD is necessary to better support policy actions. The priority areas suggested were:**

    1. More research data and monitoring of epidemiological and toxicological studies of HBCD, especially in humans.
    2. More research data and monitoring of the concentration of HBCD at the target organ. Individual HBCD isomers need to be studied separately.
    3. More research data and monitoring of exposure to HBCD, especially human exposure and exposure to the general population.

- **Suggestions for improving knowledge could be:**

    1. More research must be required from the industry itself that produces HBCD.
    2. Better organized research, collaboration between universities and specific laboratories for required research studies.
    3. Decisions taken and more money invested by policy makers in the required research.

    Better information on alternative substances is needed.

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WORKSHOP REPORT FOR PHTHALATES

KEY MESSAGES

Policy context

- Phthalates are widely used in products as additives to PVC products such as food packaging, medical devices, solvents in cosmetics, insecticides and pharmaceuticals or construction materials.

- The major source for the general population is ingestion of food contaminated through production, processing and packaging. Other significant sources are indoor air exposure and cosmetics.

- Persons under intensive care and especially neonates are highly exposed via medical devices.

- Despite uncertainties and differences between various phthalates in respect to the toxicokinetic behaviour the concentrations in children are approximately two fold higher than in adults. Altogether a significant proportion of the population is continuously exposed to these compounds.

- Toxicological effects observed in animal studies include serious effects such as disruption of hormone levels and reproductive toxicity, foetal death, cancer, liver and kidney injuries.

- Phthalates can cross the placenta leading to exposure of the foetus that is followed in early life by exposure via the milk.

Policy options

In order to evaluate the state of the current scientific knowledge and highlight important policy considerations, experts were approached by two questionnaires followed by a workshop (six experts). Based on the answers from the questionnaires and discussion at the workshop, it was concluded that:

- Experts disagree on whether or not the knowledge currently available is sufficient to justify policy action at this point. A majority of experts participating in the workshop feel that while phthalates are not persistent or bioaccumulative the continuous and daily exposure is leading to an exposure scenario that is in its practical effects similar to those with persistent and bioacumulative compounds. According to this group of experts this is enough to justify a ban for the use in medical devices. One expert felt that more data are required before a decision to change the status quo is justified.

- There is limited knowledge on many aspects of the wide range of different phthalates, but the information available causes concern and speak in favour of more research. More end-user oriented research and monitoring should be funded in order to better understand the health risks.

- The experts selected three priority areas for which more knowledge will support better understanding:

    - The extent of intrauterine exposure in humans in the first trimester of pregnancy.
    - The extent and sources/processes of occupational exposure that will add to the already high oral exposure.
    - Toxicological data on proposed replacement products and the issue of mixture effects.

- More toxicological data should be required from industry. Also, research collaborations between independent institutions could be organised at the European level.

- Effort should also be put on research on potential alternative substances to phthalates.

EXECUTIVE SUMMARY

Situation

Phthalates are a family of industrial chemicals, which have been used for a variety of purposes such as plasticisers that impart flexibility and durability to polyvinylchloride (PVC) products. They are also used in solvents, lubricating oils, fixatives and as detergents in personal care products. When incorporated into PVC, phthalates are not chemically bound and are therefore easily released into the environment consequently resulting in animal and human exposure (Kavlock et al., 2006).

Annually more than 3 million metric tons of phthalates are used globally, and because of the widespread use, ubiquitous and constant environmental presence exposure of humans, domestic animals and wildlife is virtually unavoidable. Uses of the various phthalates mainly depend on their molecular weight (MW). Higher MW di (2-ethylhexyl) phthalate (DEHP), di-isononyl phthalate (DiNP), and di-isodecyl phthalate (DiDP) are used in construction materials, and numerous PVC products including clothing (footwear, raincoats), food packaging, children's products (toys, grip bumpers), and medical devices. Relatively low MW phthalates such as di-methyl phthalate (DMP), di-ethyl phthalate (DEP), and di-n-butyl phthalate (DBP) tend to be used as solvents and in cosmetics, insecticides and pharmaceuticals, but are also used in PVC (Heudorf et al., 2007).

Background

In the general population the major source of human exposure is through ingestion of food contaminated through production, processing and packaging. Other significant sources are indoor air exposure and possibly via cosmetics. Humans may also be exposed to high doses of phthalates from medical devices during medical procedures such as blood transfusions and hemodialysis. Phthalates and their metabolites were detected in the indoor environment, consumer products, human urine, breast milk, and amniotic fluid (liquid that surrounds and is ingested by the unborn baby). Furthermore, phthalates are also able to cross the placenta, and foetal exposure is closely correlated with maternal exposure (Kavlock et al., 2006; Lyche et al., 2009).

Phthalate esters possess endocrine disrupting properties and exposures to high concentrations were shown to induce foetal death, cancer, malformations, liver and kidney injury and reproductive toxicity in

animals (Hauser and Calafat, 2005; Lyche et al., 2009). In humans, particular concerns have been raised regarding adverse effects following exposure to phthalates during development. Phthalates cross from maternal blood into the developing foetus via placental transfer and into neonates via breast milk, and these exposures may affect the developing endocrine system, which is essential for diverse biological functions including, sexual development and reproductive functions in adults (Kavlock et al., 2006). The adverse effects observed in animals raise concerns as to whether exposure to phthalate esters in the environment represents a potential health risk to humans. The observed high sensitivity of the prenatal developmental stage for endocrine disruption has led to the postulation that increased incidence of human reproductive deficits may be produced by exposure to environmental chemicals during foetal and/or pre-pubertal life (Sharp and Skakkebaek, 2008).

To identify knowledge gaps and potential agreement or disagreement on the different aspects of the phthalates issue a causal diagram illustrating scientists' current understanding of the cause-effect relationship between the production and use of phthalates, especially DEHP and its potential impact in health was made. The diagram was based on the latest review articles and reports available. A group of experts was asked to express their confidence in the current knowledge in the different parts of the diagram by completing an online questionnaire. From these experts a group of six was selected to complete a second questionnaire and take part in an expert panel workshop where the implications of the results of the two different evaluations for policy and health were discussed. Priorities for further action were identified and the workshop aimed at arriving at a final expert advice for policy makers.

Assessment

In developing an expert advice on phthalates for policy makers an important issue was prioritizing the elements of the causal diagram with respect to public health risk. This was done in an expert workshop held in Copenhagen in May 2009; six experts participated in this workshop. The ambition was to set priorities for policy uptake.

The priority knowledge gaps

The top area issues that the expert work shop considered to be the most influential for the health impact of phthalates were identified:

Intensive medical care especially of neonates is known to lead to uptake in patients far exceeding TDIs (Koch et al., 2006; Lyche et al., 2009) and there are already phthalate-free replacement products with identical properties for medical applications available (Pak et al., 2007).

There is certainly a need for more research in these areas, also monitoring of levels in humans should be a tool to get a better overview of the exposure situation (Fromme et al., 2007).

Intrauterine exposure was another important area that should be prioritized as this potentially leads to exposure during critical windows of development leading to life-long health effects (Latini et al., 2006; Mose et al., 2007.

There is still too little knowledge on potential sources and the extent of occupational exposure in humans that will add to the uptake from food and dust that is already exceeding TDIs in a considerable part of the population (EFSA, 2005; Fromme et al., 2007).

Mixtures need to be tested as for some phthalates cumulative effects on relevant endpoints such as testosterone production and testicular histopathology have been described (Lyche et al., 2009.

Also, toxicological health effects were considered, as an important area to prioritize and pushing the use of alternatives where available and spreading information on improper use of materials containing phthalates are other areas that should get attention (Lyche et al., 2009).

Most experts in the work shop have medium to very high *confidence in science* coming up with usable or decisive knowledge within the next five years. Experts show medium to high *confidence in policy actions* to effectively be able to manage the health risks of phthalates, that is that policy actions are technically feasible now, or will become technically (not politically) feasible within the next five years.

Weight of knowledge

Arguments for using the precautionary principle to ban or restrict the use of phthalates would be the already high proportion of the general population exceeding TDIs combined with the uncertainties and potential threats in the "priority elements" as described above. The effects observed in animal studies involve reproductive development and hormone levels, which are serious effects (Lyche et al., 2009). There is also a risk that other effects appear at lower doses; further research is needed to investigate this. In that case the high environmental concentrations will have even more extensive consequences. Lessons from earlier used persistent compounds should favour precaution also for less persistent compounds where common exposure routes lead to an almost continuous exposure. For some uses, alternative compounds exist, which at least are less likely to leach out of the products they are used for.

On the other hand there are arguments against a ban. The industry may take into use compounds, which are less studied and not toxicologically tested at all. Also it may be claimed the existing knowledge does not generate enough understanding to justify a ban, e.g. the current human toxicology data are insufficient to evaluate the prenatal and childhood effects following phthalate exposure.

In the panel of experts, 1 expert was against a ban whereas 5 were in favour of a ban.

Recommendations

Due to the fact that there are substantial gaps in knowledge in both phthalate levels of exposure and consequent health effects in humans, additional research is warranted.

1) It is of key importance to improve the knowledge of human toxikokinetics and toxicity, specifically during pregnancy and the nursing period, because *in utero* and early postnatal exposure appears to be the most vulnerable period during development.

2) Well-designed follow-up studies of reproductive system development and functions in the most heavily exposed and most vulnerable human populations may address the question of whether phthalates produce adverse human reproductive effects. Reproductive developmental toxicity is well studied in male animals. However, data on female reproductive toxicity are scarce and need further research. Further *in vitro* and *in vivo* studies are also warranted to improve the understanding of the modes of action of phthalates in humans.

3) Most studies focused on adverse reproductive and developmental effects associated with exposure to single phthalates. However, because humans are exposed to mixtures of phthalates both concurrently and sequentially, and available experimental evidence suggests that mixtures of phthalates may induce endocrine disruption in a cumulative fashion, it is necessary to initiate studies, which focus on mixture effects.
4) Phthalates should not be used in any medical device.

5) Despite the need for more knowledge on key issues regarding phthalates, most experts in our panel think that the weight of current knowledge legitimizes policy actions that will strongly reduce phthalates in our daily lives.

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