Chapter 2: Nature of environmental health hazards

2.1. Overview of environmental health hazards

2.2. Question “can”

2.3. What’s in this stuff?

2.4. Problem-solving exercise: environmental estrogens
2.1. Overview of environmental health hazards

⏰ Time: 45 minutes

✔️ Objectives:
At the end of the exercise, students will be able to:
1. List the environmental/occupational factors that may cause health effects.
2. Provide examples of hazards in their countries.

☞ Procedures:
(Note to instructor: The hazards chart may be generated in conjunction with Chapter 2 and used again later in the course, e.g. with Chapters 8 or 10.)

1. Ask the group to define the difference between environmental and occupational hazards. Emphasize the overlap between the two areas.

2. Put up a chart on the blackboard or wall using large pieces of paper. The column headings should be different types of hazards, but leave the columns blank. The headings should include: Biological, Physical, Chemical, Mechanical and Psychosocial hazards.

3. Ask students to brainstorm examples of environmental and occupational hazards in their country and the category to which the hazards belong. Fill in the chart on the basis of the students’ comments.

4. See example of what a completed chart could look like (on next page). Fill in additional items that have not been mentioned by the group. Note that certain hazards may fall into more than one category.

5. Discuss the utility of the this framework for hazard classification. In some cases, hazards may be more appropriately categorized by route of exposure, or setting of exposure, rather than type of agent.

📖 Materials:
Large pieces of (flip chart) paper, coloured markers, masking tape.
<table>
<thead>
<tr>
<th>PHYSICAL</th>
<th>CHEMICAL</th>
<th>BIOLOGICAL</th>
<th>PSYCHOSOCIAL</th>
<th>MECHANICAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Noise</td>
<td>Solvents</td>
<td>Animals (rodents, wild stock, wild animals, pets as allergens)</td>
<td>Lack of recognition for one’s work</td>
<td>Repetitive movement</td>
</tr>
<tr>
<td>Lighting</td>
<td>Acids/ caustics</td>
<td>Bacteria</td>
<td>Low pay</td>
<td>Poorly designed equipment</td>
</tr>
<tr>
<td>Radiation</td>
<td>Metals (lead, cadmium, mercury)</td>
<td>Viruses</td>
<td>Production pressures</td>
<td>Heavy (improper) lifting</td>
</tr>
<tr>
<td>Vibration</td>
<td>Dusts (asbestos, silica, wood)</td>
<td>Spores/ fungi</td>
<td>Boring, repetitive tasks</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>Pesticides</td>
<td>Insects</td>
<td>Stress</td>
<td></td>
</tr>
<tr>
<td>Electricity</td>
<td>Air pollutants/particulates</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2.2. Question “can”*

*The “question can” is a box or envelope used to store questions written on small pieces of paper. These will be selected at random by participants as part of the exercise.

 dó **Time:** 1 hour

✓ **Objectives:**

(Nota to instructor: This exercise may be used to initiate a new topic and assess students’ background understanding of the topic, to review a topic already covered, or to evaluate students’ learning and facilitate their self-evaluation.)

At the end of the exercise, students will be able to:

1. Explain key concepts and content areas in environmental health.
2. Evaluate their own learning (when topics are being reviewed).

✍ **Procedures:**

1. List key terms or concepts in a particular topic area or prepare questions which review the key concepts and content areas or develop short hypothetical scenarios which require participants to solve a problem by applying new knowledge or concepts. Write each term, question or scenario on a separate piece of paper and deposit it in your “question can”. (A cardboard box may serve as a question can. A large envelope may also be used.)

2. Divide participants into small groups and invite each group to pick a question from the can. All groups have a few minutes to come up with a response to their questions or a discussion of the term picked.

3. Ask the first group to read their question and to answer it. Following their response, other groups can add or correct. The instructor summarizes the correct answer and proceeds to the next group.

4. When all groups have responded, begin another round. There can usually be two or three rounds picking questions and answering them.

Alternative

Conduct the exercise in plenary. Invite one student to pick an item from the can and to define the term or answer the question posed. Other students are then asked to join in, as above. Following a brief discussion and agreement on the correct answer, (or adequate discussion of the term) proceed to the next student.
Materials:
Terms or questions on slips of paper, can (box or envelope).
Sample terms and concepts for Chapter 2 (next page) and Chapter 11.1.
Question “can”  
Sample terms and concepts  
Chapter 2*

<table>
<thead>
<tr>
<th>Hazard</th>
<th>UV-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vector</td>
<td>Hypothermia</td>
</tr>
<tr>
<td>Minimal infectious dose</td>
<td>Potential years of life lost (PYLL)</td>
</tr>
<tr>
<td>Toxicity</td>
<td>Repetitive strain injuries</td>
</tr>
<tr>
<td>Aliphatic hydrocarbons</td>
<td>Electromagnetic field</td>
</tr>
<tr>
<td>Aromatic hydrocarbons</td>
<td>Becquerel</td>
</tr>
<tr>
<td>Risk</td>
<td>Barometric pressure</td>
</tr>
<tr>
<td>Zoonoses</td>
<td>Heat stroke</td>
</tr>
<tr>
<td>Agar plates</td>
<td>Osteoporosis</td>
</tr>
<tr>
<td>Halogenated hydrocarbons</td>
<td>Ergonomics</td>
</tr>
<tr>
<td>Unsaturated hydrocarbons</td>
<td>Active versus passive prevention strategies</td>
</tr>
<tr>
<td>Endocrine disruptors</td>
<td>Stress</td>
</tr>
<tr>
<td>Organic solvents</td>
<td>Haddon’s matrix</td>
</tr>
<tr>
<td>Metabolized</td>
<td>LD 50</td>
</tr>
<tr>
<td>Metastases</td>
<td>dB(A)</td>
</tr>
<tr>
<td>Ames test</td>
<td>Alpha radiation</td>
</tr>
<tr>
<td>White finger disease</td>
<td>Ionization radiation</td>
</tr>
<tr>
<td>Stochastic effect</td>
<td>Non-Ionizing radiation</td>
</tr>
<tr>
<td>Biotransformation</td>
<td>Sievert</td>
</tr>
<tr>
<td>Lipophilic</td>
<td></td>
</tr>
</tbody>
</table>

* Definitions can be found in the text
2.3. What's in this stuff?

 предлагаемая длительность: 30-45 минут

**Objectives:**

At the end of the exercise students will be able to:

1. List the key chemical and physical properties that determine a substance's toxicity.
2. Define the information one should have about a chemical before using it.

**Procedures:**

1. Introduce the following role-play and seek two volunteers to play the manager and the salesman:

   "You are a manager of a factory that extensively uses solvents in your processes. A representative from a company that has supplied you with chemicals in the past has called to tell you that his company is making a new product that would be great for your company's needs. What questions do you ask him?"

2. Allow 5-10 minutes for the role-play and then invite additions or corrections from the class.

3. If not mentioned, indicate that the manager should want to know not only about the effectiveness of this product and how it will enhance productivity, but also about its potential health effects on the workers who will be using it and its environmental impact.

The information that should be sought includes:

- What is in it?
- How much is too much? (What dose or quantity of the product is recommended for safe use?)
- What are its potential health effects in the short and long term?
- What kind of protective equipment is required? Are there any other precautions?
- Is it flammable, explosive, reactive, etc? Are there any special recommendations with regard to storage?
- What should be done in case of emergency (respiratory or dermal exposure, spills)?
- How can the product be safely disposed of?
- Is there another product which is less toxic that can be used instead?
For a complete list of chemical and physical properties, refer to a sample "Material Safety Data Sheet".

4. Summarize and conclude the exercise.

**Alternative**

Label a container with the name “Brand X”. Tell the class that they are a group of workers who will be working with this product from now on. What would they like to know about it? List their answers on a flip chart.

📖 **Materials:**

Flip chart, coloured markers, tape.
2.4. Problem-solving exercise: environmental estrogens
Prepared by Evert Nieboer

 lamps

 Time: Two 1-2 hour sessions, allowing time for home study

(Note to instructor: This exercise is designed to be used at the end of Chapter 2 and again at the end of Chapter 3. It is often desirable to distribute Part I of the exercise (Chapter 2) and encourage students to meet outside the classroom, then come to class prepared to discuss the case. This should be repeated again with respect to Chapter 3.)

✓ Objectives:
At the end of the exercise, students will be able to:

1. Understand the basic principles of reproductive and developmental toxicology of DDT and polychlorinated biphenyls (PCBs), persistent organic pollutants (POPs) as a group of toxic chemicals, estrogen mimicry, molecular biology of cancer, classification of carcinogens, epidemiological study designs, rules of causation, selection bias and confounders, and the weight-of-evidence approach.

2. Recognize the need for a critical assessment of available evidence and for using a weight-of-evidence approach in classifying environmental pollutants.

3. Distinguish between research hypotheses and factual knowledge.

4. Appreciate the built-in uncertainties in epidemiological studies.

5. Promote an understanding by the public of the uncertainties and limitations inherent in risk assessment methodologies. Encourage a willingness by the public to participate as subjects in environmental health studies.

☞ Procedures:

(Note to instructor: This exercise requires substantial study by participants, both in the classroom and at home. Divide the workload of retrieving and reviewing references among the class members. A debriefing session is recommended to provide a context for addressing the various questions posed below. Review of Chapters 2 and 3 is, of course, a prerequisite. Additional references to those provided might also be consulted, especially the general references to PCB literature given in the “Emergency Response to a PCB fire” problem scenario.)

* Dr Evert Nieboer, Department of Biochemistry, McMaster University, Hamilton, Ontario, Canada
1. Introduce the exercise and review its objectives. Divide participants into small groups (4-6 people). Instruct participants to identify a chairperson and a recorder.

2. Distribute the exercise and review the participants' tasks.

3. Reconvene the groups and invite a response from one group to the first question. Ask whether other groups have different responses. Summarize and, if necessary, expand on the participants' responses and proceed to the next question. Allow a different group to initiate the discussion and continue in this way until all questions have been answered. Possible answers are provided below. These answers are not all-inclusive. Instructors are encouraged to develop alternative responses and intervention strategies that are appropriate to the local situation.

4. Summarize the results, emphasizing key messages. The decision to proceed to Part II should be made jointly by the students and instructor.

**Materials:**

Problem-solving exercise (Annex 5), flip chart, coloured markers, reference documents for classroom review.

---

**Case scenario, background**

Steroid hormones are essential for the growth, differentiation and function of many tissues in both animals and humans. The International Agency for Research on Cancer (IARC) (1987) designates steroidal estrogens as used in estrogen replacement therapy as carcinogenic to humans. The risk of endometrial and breast cancers is increased. Environmental estrogens (xenoestrogens) bind to estrogen receptors and have estrogenic activity in model systems. As illustrated in Box 2.1, this group of chemicals includes nonsteroidal estrogens, polycyclic aromatic hydrocarbons, DDT, and a number of PCBs (congeners that have two adjacent nonsubstituted carbon atoms on at least one of the biphenyl rings, including a *para* position). In addition to being suspected of acting as promoters in the development of estrogen-mediated cancers in humans (Davies et al., 1993), such xenoestrogens are believed to disrupt the immune, nervous and endocrine systems (McLachlan, 1993; EHP, 1995). Considerable and convincing evidence exists that reproductive and developmental processes are impaired in wildlife (such as birds, fish, reptiles and mammals (Colborn and Clement, 1992; Colborn et al., 1993). Comparable causal links in humans are less convincing and still speculative, such as the role of xenoestrogens in an apparent decline in semen quality over the past 50 years (Sharpe and Skakkebaek, 1993; Carlsen et al., 1995; Sate, 1995). The evidence for the involvement of environmental estrogen mimics in the etiology of breast cancer is explored in the present case scenario.
Case scenario, Part I

In a recent prospective cohort study investigating the role of endogenous hormones and environmental factors in cancer development, 58 women with a diagnosis of breast cancer 1-6 months after they entered the cohort (14 290 participants from New York City, 80% Caucasian) were compared to 171 controls selected from the same cohort and matched for menopause status and age. Sera, taken at the time of enrolment between 1985 and 1991 when attending a mammography screening clinic, were analysed for a metabolite of DDT [2,2-bis(p-chlorophenyl)-1,1,1-trichloroethane], namely DDE [1,1-dichloro-2,2-bis(p-chlorophenyl)ethylene], and total PCBs (polychlorinated biphenyls). Limits of detection were 1 µg/L for DDE and 2 µg/L for total PCBs based on three times the standard deviation of the results from the lowest quality-control serum pool standard over the course of the analyses (n=18). DDE was 35% higher in patients than in control subjects (p=0.031), while PCBs were 15% higher (p=0.058). After adjustment for first-degree family history of breast cancer, lifetime lactation and age at first full-term pregnancy, conditional logistic regression analysis showed a four-fold increase in relative risk of breast cancer for an elevation of serum DDE concentrations from 2.0 ng/mL (10th percentile) to 19.1 ng/mL (90th percentile) (p=0.0037 for trend). Other potential confounders considered, but with no effect, were: body mass index, age at menarche, history of benign breast tissue, history of tobacco smoking and/or alcohol drinking, and race. The corresponding association for PCB levels was not significant (p=0.16). It was concluded that environmental chemical contamination with organochlorine residues may be an important etiological factor in breast cancer.

Chapter 2 Questions

1. **In simple terms, describe how estrogens regulate the growth, differentiation or function of cells.**

The estrogen molecule must first diffuse across the cell membrane, and subsequently seek out a special protein, called its receptor, to which it binds (see Box 2.1). The estrogen-receptor complex then diffuses into the cell nucleus where it seeks out a binding site on DNA corresponding to a specific gene. This action is crucial to beginning a process called transcription, which is the synthesis of the messenger (mRNA). The information on the mRNA is sufficient to synthesize a specific protein or enzyme. This step is followed by an altered functional response such as those mentioned in the question. Xenoestrogens can mimic the role described for endogenous estrogens, resulting in up or down regulation.

2. **DDE and PCBs are persistent organic pollutants (POPs). What is meant by this?**

POPs are considered persistent because they tend to be resistant to biological, chemical or photolytic breakdown (see Box 2.2). Consequently they remain in the environment for many years. For example, as much as 50% of DDT and related compounds can remain in the soil for 10-15 years after application. For PCBs, the environmental persistence increases with the degree of chlorination, although half-times (t½) range from 10 days to 1.5 years for photo-degradation. In organisms, DDT is relatively persistent but its hydrolysis product DDE is much more so. In humans, DDT has a t½ value of 1.7 years while that of DDE is 6-8 years. PCBs have t½ values of 125-350 days, depending on the degree of chlorination.
3. **How is DDT converted to DDE?**

DDT is converted by biotransformation to DDE, which requires a specific enzyme (a dehydrochlorinase). HCl, hydrochloric acid, is removed from the >CHCCl3 group that joins the two benzene (phenyl) rings to give the >C=Cl2 moiety.

4. **What is the likely source or exposure route of the organochlorines?**

In the absence of special sources such as occupational exposures, the diet is the main source of PCBs and DDT. Primary sources are animal fats, eggs and fish. Ingestion is therefore the primary route of intake.

5. **Comment on the use of serum PCB and DDE levels as measurements of exposure.**

Because of the relatively long half-times in blood, serum PCBs and DDE should reflect the steady state levels in tissue lipids, unless a recent exposure has occurred. Because the organochlorines are associated with serum lipids, it would be more precise to express their concentrations in terms of the total lipid content of the serum samples, since the latter varies from person to person. A single measurement does not constitute a reliable assessment of body burden, and several samples might have been collected over an extended period of time. See also answers to Chapter 3, Question 5.

6. **From the toxicokinetic perspective, does it make sense that duration of lactation is an important determinant in the study? Explain.**

PCBs and DDE are secreted into breast milk. There is some evidence that maternal serum concentrations decline with longer duration of lactation.

**Chapter 3 Questions**

1. **The study considered in the scenario is a case-control study nested within a prospective cohort study. What are the salient features of these two types of epidemiologic study?**

See Section 3.2. Chapter 3 of the WHO Basic Epidemiology text is also very helpful.
2. **What are confounders?**

Confounding occurs when two risk factors or exposures have not properly been separated and the effect is assigned only to the variable considered. The confounder must be associated with both the disease and the exposure being studied. Confounders have been considered quite adequately in the study of the case scenario.

3. **Has selection bias been avoided?**

Since the women in the original cohort were enrolled while attending a mammography screening clinic, a true representation of females in the general population may not have been attained and selection bias may have occurred.

4. **What are the known risk factors for breast cancer?**

Known risk factors for breast cancer include genetic factors (first-degree relatives), endocrine factors (early age of menarche, late onset of menopause, nulliparity and low parity, late age at first pregnancy, exogenously administered estrogen hormones) and environmental factors (dietary fat or caloric intake; moderate alcohol intake).

5. **Apply the rules of causation outlined in Table 3.3 to the study at hand.**

The rules of causation are summarized in Table 3.3.

Temporal relation: Since the cancer cases were diagnosed 1-6 months after entry into the cohort, the organochlorine level measured corresponds to a situation where almost all the patients had breast cancer at the time of sampling. Since the latency period for breast cancer is 5-20 years, the serum PCBs or DDE assessments do not reflect the exposure during the critical early phases of the development of the disease.

Consistency: Three other case-control studies suggest weak links between environmental organochlorine exposures and breast cancer risk, but a fourth comprehensive study was negative (Wolff and Toniolo, 1995). Nor do much higher occupational exposures suggest this association (IARC, 1987; Safe, 1995).

Strength: The relative risks are low, so if the effect is real it is weak.

Study design: A case-control study is appropriate for identifying a causal link to a specific exposure.

Dose-response relationship: There is a response gradient for DDT (DDE), but not for PCBs.

Plausibility/correlation: Evidence from animal data for the carcinogenicity of both DDT and PCBs is “sufficient” (IARC, 1987).
ANNEXES

Mechanism of action: The estrogen mimicry hypothesis is believed to explain the role of these organochlorine compounds as promoters of cancer. Estrogenicity tests indicate that some PCBs and DDT are weakly estrogenic, but surprisingly DDE is not (Safe, 1995).

Reversibility: No data is available.

6. **Comment on the authors’ overall conclusion. Is it valid?**

Considering that none of the tests shows strong causal links, the evidence may be said to be at most equivocal.

---

**Case scenario, Part II**

Two of the investigators of the study described in Part I, participated in a second study conducted in California (Krieger et al., 1994; also see Wolff and Toniolo, 1995). Again the hypothesis tested was that exposure to organochlorines is a risk factor for breast cancer. Study subjects belonged to a cohort of 57,040 women (46,629 white, 8,123 black and 2,288 Asian) who took a multiphasic health examination between 1964 and 1971, independent of concern about risk of breast cancer. Follow-up was conducted through December 31, 1990 to identify those with histopathologically confirmed primary breast cancer six or more months after their multiphasic examination. From among the women who developed breast cancer (1,805 white, 230 black and 62 Asian), a random sample of 50 women in each racial/ethnic group was selected, as were equal numbers of controls matched according to race/ethnicity, date of joining the medical care programme, year of multiphasic examination and age at that time, and length of follow-up. Matched analyses found no difference in DDE or total PCBs, although organochlorine levels were significantly higher (p<0.05) among black and Asian women compared to white women. The mean differences (95% confidence intervals) for DDE were 11.0 (4.3, 17.6) ug/L in the black women and 12.6 (4.3, 17.6) ug/L in the Asian women and, respectively, 0.8 (0.2, 1.4) ug/L and 1.4 (0.8, 1.9) ug/L for PCBs. The detection limits were as stated in Part I. These ethnic differences persisted even after adjusting for available confounders: age at and year of medical examination, body mass index, educational level, poverty level, place of birth (United States or elsewhere), pregnancy history (ever or never). Multivariate analysis showed the absence of a significant association (p<0.05) between exposure to organochlorines and breast cancer, regardless of length of follow-up, year of diagnosis and menopausal status. The conclusion was that the data do not support the hypothesis that exposure to DDE and PCBs increases risk of breast cancer.

---

**Chapter 2 Questions**

1. **What do we know about the molecular basis of cancer?**

Like other cancers, breast cancer appears to require a number of events at the level of genes corresponding to the conversion of proto-oncogenes to oncogenes, or inactivation of pairs of homologous (the copy inherited from the mother and that received from the father) suppressor genes. An oncogene is a gene capable of inducing one or more aspects of the neoplastic phenotype, with the proto-oncogene the normal (healthy) cell homologue. Proto-oncogenes act as central regulators of cell growth (proliferation) and differentiation (progressive diversification in cellular structure and function during the development of an organism). Suppressor genes are genes whose loss of function leads to one or more aspects of the neoplastic phenotype; in normal cells, they effectively act as repressors of biochemical function and cell growth, but this “braking” ability is lost when both copies of the gene are inactivated and thus results
in uncontrolled growth. The genetic events mentioned account for the various phases of cancer development: initiation, promotion (cell proliferation), progression (different histological changes) and metastases (spreading). Although such gene damage can occur spontaneously, certain environmental chemicals can inflict it and these are said to be genotoxic. Estrogens are believed to act as cancer promoters by enhancing cell division, thereby increasing the probability that a genetic lesion will occur (Cooper, 1995).

2. **Do you have any analytical concerns about the PCB and DDE measurements reported in Parts I and II?**

As already indicated in the answer to Question 5 above (Case scenario, Part I), it would have been better to express the PCB and DDE concentrations relative to the total serum lipid content. Further, the collection and analysis of a single sample at a point when the disease has already occurred is a poor way of establishing causality. Thirdly, the detection limit for total PCBs is comparable to the actual concentrations found. This fact is not very reassuring.

3. **Does the estrogen hypothesis make biological sense to you (e.g. in terms of nutrition or physiology)?**

Safe (1995) shows that environmental organochlorine estrogens contribute an infinitesimal amount to the dietary intake of estrogenic substances, when expressed in estrogen equivalents and compared to intakes of flavonoids in foods or that received in birth control and postmenopausal therapy regimens. Unique disruption of endocrine pathways must therefore occur for xenoestrogens to be effective.

**Chapter 3 Questions**

1. **Is there room for an environmental risk factor to explain breast cancer?**

Since the genetic events that lead to breast cancer are often determined by gene-damaging (genotoxic) agents or cancer promoters (epigenetic toxicants), environmental exposure provides a plausible pathway.

2. **Does the "xenoestrogen hypothesis" of breast cancer make epidemiological sense? Return to your previous deliberations concerning the rules of causation. You might also consider that epidemiological studies of individuals occupationally exposed to much higher concentrations of PCBs or DDT/ DDE do not show a higher incidence of breast cancer (IARC, 1987; Safe, 1995).**

Although the Part II study has improved power because of the larger number of cases considered, the ratings for the other tests diagnostic of causation are not upgraded. It is doubtful whether a real risk could have
been detected. Therefore the conclusion that the data do not support a causal link is again equivocal.

3. **IARC (1987) designates DDT as Group 2B and PCBs as Group 2A carcinogens. Do the results of the two studies discussed suggest that these classifications ought to be upgraded? Justify your answer?**

Clearly, the epidemiological (human) evidence will remain limited for PCBs and inadequate for DDT, and no upgrading to Group 1 (designated as carcinogenic in humans) for PCBs or to Group 2A (sufficient animal evidence and limited human evidence) for DDT is in order.

**Selected references**


Sharpe RM, Skakkebaek NE. Are estrogens involved in the falling sperm counts and disorders of the male reproductive system. Lancet 1993; 341:1392-1395.


Learner, peer and problem evaluation

Formative evaluation

At the end of each session, but especially after the last one, allow participants to express their thoughts and feelings about their own participation and progress, as well as about the contributions and roles of the instructor/facilitator and fellow learners. Solicit comments about the approaches used (i.e. debate, role-playing, other). A written or oral evaluation concerning achievement of the stated objectives is also a good idea. Can the problem as presented be improved? How?

Summative evaluation

An assessment of the factual knowledge associated with Chapter 2 questions might best be achieved by short answer questions (SAQs) or multiple choice questions (MCQs). Both approaches have acceptable reliability (are the results reproducible on different occasions or by different assessors?) and validity (does it measure: the intended characteristic or learner attribute in the present context, factual knowledge, application of knowledge and reasoning ability?). An effective approach to SAQs is to have a brief description of a real event or observation in which concepts and terms are used in context. Specific answers can then be solicited (e.g. what are estrogen receptors and how do they work?). MCQs also start with a brief description, which is usually followed by a list of alternative answers from which the correct answer(s) should be selected. Evaluation related to Chapter 3 questions might involve the critical evaluation of a recently published epidemiological study, or application of the rules of causation to it. Alternatively, the weight of evidence for a suspected association of an outcome (e.g. human carcinogenicity) to exposure to a specific contaminant might be reviewed.