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Contents

| | | |
|------|---|-----|
| 24.1 | Introduction: What Is Environmental Medicine? | 549 |
| 24.2 | External Processes: How Are We Exposed to Hazardous Substances? | 549 |
| 24.3 | Internal Processes: How Does the Body Respond to Hazardous Substances? | 551 |
| 24.4 | Toxicology and Epidemiology: How Is Environmental Medicine Studied? | 556 |
| 24.5 | Health Protection: How Can Adverse Effects Be Minimized? | 561 |
| 24.6 | Case Study: Arsenic | 563 |
| | Further Reading | 566 |

24.1 Introduction: What Is Environmental Medicine?

A broad definition of environmental medicine is the study of how the environment affects health, including the characterizing of exposures, and the practice of how to minimize any adverse effects. The term environmental medicine is effectively synonymous with the term environmental health, except that the latter term is often confused with “health of the environment,” so we will stick to the former term. The word environment also requires interpretation, because there are many subsets of environments that have special branches of environmental medicine associated with them. For example, occupational medicine (the study of the effects of the work environment on health) and social medicine (the study of the effects of social structures and dynamics on health). Of particular interest in this book are those aspects of the environment that relate directly to substances and processes of geological origin. This chapter will attempt to provide a brief outline of the principles and practice of environmental medicine by drawing largely on examples with geological relevance.

24.2 External Processes: How Are We Exposed to Hazardous Substances?**24.2.1 Environmental Media**

A medium (pl. media) is a vehicle by means of which exposure occurs. Thus, when humans are exposed to arsenic (for example), it is often by means of their drinking water, that is, water is the environmental medium of exposure. Other media by which substances of geological origin may come into contact with humans include air (e.g., inhalation of radon gas or airborne particulates), soil, and food. Although there is some direct ingestion of soil in food preparation or in conditions such as pica, contaminants in

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Table 24.1 A simple framework for classifying health effects of the environment

| Environmental medium | Health effect | Type of example from medical geology |
|----------------------|---------------|---|
| Air | Physical | Death by asphyxiation: absence of oxygen in a mine shaft; chronic obstructive pulmonary by disease caused inhalation of particles |
| | Chemical | Neurotoxicity by inhalation: geothermal hydrogen sulfide accumulated in basement |
| | Biological | Pneumonia: infection by airborne anthrax from dried out soils |
| Water | Physical | Death by drowning: inundation by tsunami or other flooding |
| | Chemical | Skin cancer and vascular pathology: chronic ingestion of arsenic in drinking water |
| | Biological | Meningitis: infection by amoebae in hot springs |
| Soil/food | Physical | Direct injury: from displacement of natural or artificial structures in earthquake |
| | Chemical | Goiter: disruption of metabolism in areas with iodine deficient soils |
| | Biological | Tetanus: infection of cuts by contact with soil containing <i>Clostridium</i> spores |

soil often enter humans by way of the food chain. Soil and food can therefore be conveniently thought of as one medium. For example, in regions where iodine is deficient in the soil, it is also deficient in the food chain, and goiter (or cretinism in children) may result as a deficiency disease in people dependent on local produce. The soil/food medium is complicated by the factor of bioavailability, which determines the ability of a substance to migrate, in its current chemical state, from the soil fraction to living organisms. (see also Chap. 27, this volume). These three environmental media: air, water, and soil/food form the basis of a useful analytic framework in environmental medicine, as illustrated in Table 24.1.

24.2.2 Hazardous Substances

To carry the analytic framework further, the nature of the injurious agent conveyed by the above media can be examined. It is in this examination that environmental medicine most clearly shows itself as a broad science; the injurious effects of landslides are just as relevant in this context as are the toxins traditionally studied by toxicologists. The latter affect health because of their chemical nature, and are arguably most readily associated with the field of medical geology. A broader perspective was illustrated in Table 24.1 with physical as well as microbiological health effects that result, however indirectly, from geological processes.

24.2.3 Mechanisms of Exposure

Given a hazardous substance that has made its way to a human through an environmental medium, it remains for that substance to exert its influence by entering into the biochemical and metabolic functioning of the body at the cellular level. First and most obviously cellular function may be interrupted at the physical level by direct cellular injury in a rockfall, or by asphyxiation as the respiratory systems fails

following a tsunami (Table 24.1). Chemical and biological substances, on the other hand, enter the body through existing organ systems, by means of which they reach the cells and organ systems that they affect. Inhalation, ingestion, and absorption are such modes of penetration to the cellular level, with the systems responsible to include the respiratory, gastrointestinal, and integumentary (skin) systems respectively. Thus carbon monoxide from incomplete coal combustion is inhaled, passes through the lungs to red blood cells in the alveolar capillaries, and irreversibly binds hemoglobin so that cells are starved of oxygen. Lead from old paint is ingested with house dust, passes through the intestinal tract where it is taken up by the bloodstream, and transported to the brain where it exerts its neurotoxic effect on brain cells. Methylmercury accidentally spilled on the skin is absorbed directly through the skin and into the bloodstream, and is likewise transported to the brain where it exerts its neurotoxic effect. An understanding of these particular mechanisms of introducing hazardous substances to the body at the cellular level are of critical importance to the practice of environmental medicine: only with such an understanding can appropriate barriers be devised to protect individual as well as public health (see also Chap. 6, this volume).

24.2.4 Case Study: Soil, Water, and Amoebae

New Zealand is located in the Pacific Ring of Fire, on the boundary of two major tectonic plates. As these rub together, a number of geothermal phenomena are produced, including volcanism (see Chap. 10, *Volcanic Emissions and Health*, this volume) and the geothermal heating of freshwater springs. Such hot springs are an integral part of New Zealand's cultural history; since the first humans colonized the islands some 1,000 years ago, hot springs have been used for recreation, cooking, healing, and heating.

About 100 natural thermal springs are dotted around the country, and they are the delight of New Zealand children and tourists alike. The diving, jumping, and water sliding

unfortunately took a serious blow in the late 1960s when isolated deaths began to occur from primary amoebic meningoencephalitis (PAM).

The amoeba responsible for PAM, *Naegleria fowleri*, invades the nasal mucosa and olfactory nerve endings, and then tracks up to the meninges and brain through a sieve-like weakness in the skull known as the cribriform plate. The infection is usually accompanied by a fever, sore throat, and headache and progresses in a few days to nausea, vomiting, neck stiffness, and sometimes olfactory hallucinations. Death is usual by day 5 or 6, and almost inevitable by day 10. Active and healthy young people are often the victims, which fuels public outrage disproportional to the public health impact of this disease (there have been less than a dozen deaths from PAM in New Zealand, and less than 200 reported cases globally).

An epidemiological association (see Sect. 24.4) was soon established between PAM and exposure to hot springs, and *N. fowleri* was isolated from water samples from suspect springs. Once the microbial hazard, environmental medium, and mechanism of introduction had all been established, appropriate barriers could be devised to protect the public from further infections. There was a publicity campaign requiring signs at hot pools to warn the public to keep their heads above water. This safety message persists in the New Zealand psyche, and many home spa users adhere to it even if they can no longer remember exactly why.

Interestingly, there is a geological link in this example because *N. fowleri* was only found in soil-contaminated waters. Free living in soil, the organism thrives in the warm waters of hot springs (and therefore not surprisingly also does well at body temperature). It is introduced into the water if the spring runs over bare soil before entering the pool, if the pool has unsealed edges or bottom allowing direct soil contact or runoff with rain, or if the pool surrounds are of exposed soil that enters the pool on bathers' feet. A second public health intervention was therefore to isolate the hydrological environment from the geological environment: standards were introduced for piping water into pools; improving pool construction; and installing wide, paved pool surrounds.

There have now been no cases in New Zealand for over 20 years. This provides an excellent example of the effectiveness of the sound practice of environmental medicine.

24.3 Internal Processes: How Does the Body Respond to Hazardous Substances?

24.3.1 Concepts of Absorption, Distribution, Metabolism, and Repair

The basic processes of absorption, distribution, and metabolism are critical in gauging the body's internal exposure and response to any toxic chemical. In particular, these processes

are crucial in understanding the significance of laboratory animal results in relation to human health risks, when modeling or estimating exposures in epidemiology studies, and when discussing the potential for increased susceptibility of subgroups within the population. Figure 24.1 depicts this relationship (see also Chaps. 7 and 9, this volume).

24.3.1.1 Absorption

Chemicals are absorbed through oral ingestion, inhalation, or through the skin at a rate relating to their water solubility, size, ionization state, acid dissociation constant (pKa), and exposure concentration. In general, ionically neutral compounds are absorbed more readily than ionized compounds. Acids tend to be better absorbed in the acidic stomach, while basic compounds may be better absorbed under the more alkaline conditions in the small intestine. When considering metals, active uptake mechanisms play an important role, such as the use of calcium transport mechanisms serving to increase the uptake of lead. Some characteristics of compounds and their influence on absorption are shown in Table 24.2.

It is thought that water-insoluble metal forms are not bioavailable for absorption by the stomach and small intestine. However, some insoluble forms become bioavailable in the acidic stomach. For example, the gastrointestinal effects for copper sulfate and copper oxide in humans are similar (Pizarro et al. 2001).

24.3.1.2 Distribution

The distribution of a chemical in the body is a function of its water solubility, ionization state, molecular size, and affinity

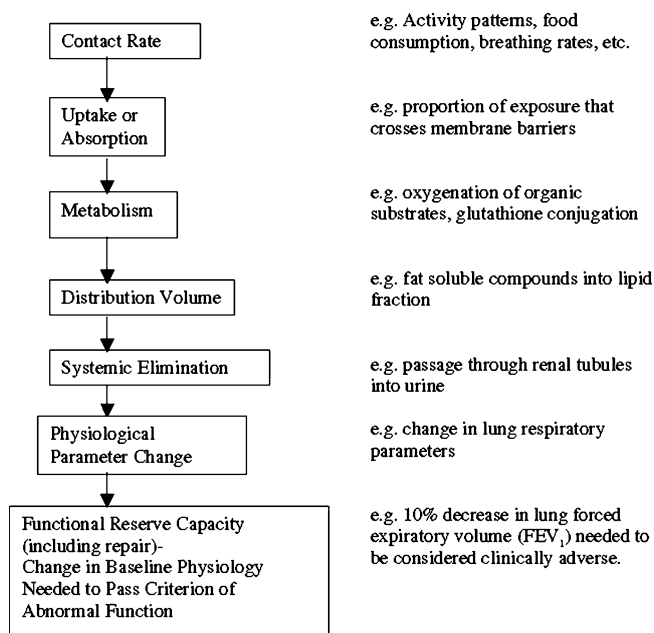


Fig. 24.1 The pathway from exposure to response

Table 24.2 Substance characteristics that influence absorption or bioavailability

| Substance characteristic | Uptake mechanism | Example |
|--|---|---|
| pH of weak organic acids and bases | Ionically neutral states are more readily absorbed | Aniline absorption in the small intestine. |
| | | Aspirin absorbed in the stomach |
| Valence states of metals | Specific active transport mechanisms | Chromium VI uptake into cells, while Chromium III is excluded Inorganic arsenic transported by phosphate transport mechanisms |
| Cationic metal form may have competitive antagonists | Specific active transport mechanisms | Lead competes with iron for uptake and reduces iron bioavailability; molybdenum competes with copper for absorption A child who gets enough iron and calcium will absorb less lead |
| Sorption status of metals in soils (bioavailability) | Ionic water soluble forms are more available | Cadmium is bound to organic counter ions in soil at high pH and therefore less bioavailable |
| Molecular weight | Smaller compounds tend to cross membranes more easily | Limited bioavailability of some large marine biotoxins (e. g., gymnodamine) through oral ingestion |
| Water solubility | Water-soluble liquids that are fat soluble cross membranes; water-soluble unionized compounds cross membranes more easily than ionized counterparts | |

for specific receptor sites in tissues. Generally, the more water soluble the compound, the more easily it can be excreted, and most metabolic processes work toward this end. Extreme cases, such as the case with DDT, can be illustrative. DDT is extremely lipophilic and therefore is retained in adipose tissue throughout the body and the fat found in the bloodstream. In cases such as this, the distribution affects the compound's toxicity and biological half-life (in this case, approximately 8 years) through storage reservoirs that prevent access to metabolic systems.

The chlorinated dibenzo-*p*-dioxins are another example of lipophilic compounds distributing into adipose tissue, and because those isomers with chlorines at the 2,3,7,8-positions are highly resistant to metabolism, the result is a biological elimination half-life of 7–11 years (U.S. EPA 2000).

The tissues of highest concentration may or may not be the critical target organs. For example, copper is stored primarily in the liver, brain, heart, kidney, and muscles. About one-third of all the copper in the body is contained in the liver and brain, and the critical toxicological effect from chronic exposure is in the liver. Another one-third is contained in the muscles, where no toxic effect is known to occur. The remaining one-third is dispersed in other tissues.

Some compounds have deep storage depots, such as fluoride or lead in bone. When the chemical is in these depots, it is not bioavailable for activity at distal sites, and the elimination half-lives of such compounds are very long. The half-life for lead in bone is estimated to be about 25 years. Lead has a half-life of about 25 days in the blood. Methylmercury has a half-life for elimination of about 50 days in adult males and females. However, infants have poor elimination of organic and inorganic heavy metals in the first 6 months prior to development of metal transport systems, and it is

possible that mercury is eliminated much more slowly in the child (Brown 2001).

24.3.1.3 Metabolism

Metabolism of a substance is subject to enormous interspecies and interindividual differences, through genetic polymorphisms, which in turn affects susceptibility to the chemical.

Metabolizing enzymes serve the functions of detoxification, intoxication, and facilitation of excretion of compounds. Key enzymes are the cytochrome P-450 family of heme-containing oxygenases, acetyltransferases, glutathione-S-transferases, and glucuronidases. These enzymes are needed to increase the polarity and water solubility and thus the rate of excretion of organic environmental contaminants.

Through metabolic enzyme differences, chemicals that are benign to humans can be highly toxic to some species and vice versa. The toxicity of paracetamol (acetaminophen) to cats is a classic example of how species-specific metabolism can influence toxicity. Cats are particularly susceptible to paracetamol intoxication because of their impaired glucuronic acid conjugation mechanism and rapid saturation of their sulfate conjugation pathway, whereas humans rely heavily on a much more robust glucuronic acid conjugation system, which effectively detoxifies the critical metabolites.

For some metals, metabolism is also influential in determining bioavailability and toxicity. Arsenic methylation, the primary process by which the metal is metabolized in the body, has generally been considered a method of detoxification. Methylated arsenicals produced metabolically from inorganic arsenicals are excreted faster and have a lower affinity for tissue sulfhydryl groups than inorganic

arsenicals, especially arsenites (Chan and Huff 1997). It has also been shown that the incidence of skin cancer due to oral arsenic exposure is associated with individual methylating capacity (Hsueh et al. 1997). The epidemiological evidence indicates that the methylation detoxification mechanism does not become saturated even at high doses but that some inorganic arsenic always remains in human urine, regardless of the amount of arsenic exposure (Hopenhayn-Rich et al. 1993). Arsenic poisoning has been thought to occur only when the rate of exposure exceeds the rate of methylation (Le et al. 2000).

24.3.1.4 Repair

The body is constantly repairing itself from damage sustained from a myriad of environmental insults. Among the most significant of these mechanisms is with the repair of genetic lesions. Genetic lesions are central to the mechanisms of carcinogenesis and some developmental defects.

There are over 100 genes responsible for maintaining the integrity of our DNA. These include endonucleases, polymerases, and ligases. Each enzyme is important in one or more areas of DNA repair, which in turn affects individual susceptibility to particular agents. The clinical manifestations of defects in one or more of these enzymes can be seen in a number of genetic diseases. Xeroderma pigmentosa (XP) patients carry a 1,000-fold increase in skin cancer incidence, but no significant increase in internal cancers. UV-light-induced single DNA base point mutations are the most critical for these patients. XP patients have a defect in a key endonuclease required for carrying out excision-repair of point mutations (Hoffman 1994). Ataxia telangiectasia patients, on the other hand, can repair point mutations induced by UV light, but are very susceptible to x-rays because of a defect in repair of strand breaks. Similarly, Bloom's syndrome patients carry a defect in DNA ligase I. This defect effectively increases chromosome fragility and results in huge increases in cancer rates (e.g., 28 out of 103 patients died of cancers at a mean age of 20.7 years).

A number of metals are carcinogens by mechanisms that are not absolutely clear, but some metals do appear to inhibit one or more DNA repair enzymes. This could be a mechanism of indirect action for several metal carcinogens.

24.3.2 Dose–Response Relationships

A critical aspect of toxicology is the description of a dose–response relationship. Conceptually, a dose–response relationship requires either the severity of a particular end point, or the incidence of the adverse effect in the population, to increase with increasing dose. The increase does not need to be monotonic, but there should be a region of the

dose range that is linear. Once much higher doses are reached, additional toxic effects of a different nature may manifest and cloud the estimation of the response at lower doses (see also Chap. 26, this volume).

For most acute toxicity end points, such as acute lethality, the dose–response relationship is described in a relatively straightforward manner, and linear or log-linear models describe these relationships quite adequately (Fowles et al. 1999).

For chronic toxicity end points, such as cancer, the behavior of the dose–response curve at the low dose end is critical to interpretation and assessment of health risks. Some compounds have associated biological mechanisms that support a “hockey-stick” shaped dose–response curve for cancer. This is particularly relevant to the case of overloading of functional reserve or repair capacity of the body at high doses.

The dose–response relationship is important for the following reasons:

- Validation of hypothetical causal relationships to chemical exposure
- Provision of a measure of toxicological potency which allows prioritization of hazards and risks by risk managers
- Description of the range of variability in responses in the test population

24.3.3 Varieties of Effects: “Non-Cancer” Toxicity and Carcinogenicity

Regulatory toxicology and toxicological risk assessment generally divides responses into those of a carcinogenic and non-carcinogenic nature.

24.3.3.1 Carcinogenicity

It has been estimated that over 80% of all cancers, population wide, are environmentally induced (Doll and Peto 1981). This estimate includes cancers from smoking, dietary carcinogens, and exposure to air and water pollution in addition to those from cosmic and solar radiation (see also Chap. 25, this volume).

One example of a type of cancer thought to have strong environmental links is prostate carcinoma (PC). In the United States, 10% of all 75-year-old men (black, white, and Japanese ethnicity) have latent PC. However, the active form of this carcinoma is 60:30:1 in these populations. This suggests that there are environmental, endocrine, or dietary factors that influence the progression of latent PC to active cancer.

Adult tissues, even those that are composed of rapidly replicating cells, maintain a constant size and cell number by regulating the rate of replication, by differentiation to

assume specialized functions, and by programmed cell death (apoptosis). Cancers are diseases in which there are somatic mutations of genes critical to maintenance of control over cell division that lead to loss of control over cell replication, differentiation, and death. The International Agency for Research on Cancer (IARC) has defined chemical carcinogenesis as: “the induction by chemicals of neoplasms that are not usually observed, the earlier induction by chemicals of neoplasms that are commonly observed, and/or the induction by chemicals of more neoplasms than are usually found.”

Carcinogenicity is thought to occur in a multistep or “multistage” process, with several key events occurring in sequence for a given normal cell to convert into a malignant cell with unregulated growth. The number of genes altered in a cancer cell compared to a normal cell is not known; recent evidence suggests that 3–10 genetic events are involved in common adult malignancies in humans. Two distinct classes of genes, proto-oncogenes and tumor-suppressor genes, are involved in the cancer process (Barrett 1993).

In the current multistage model of carcinogenesis, development of a malignant tumor occurs in three stages: initiation, promotion, and progression. Initiation involves an irreversible change in a normal cell (usually an alteration of the genome) allowing for unrestricted growth. The initiated cell may remain latent for months or years. During this period of latency, the initiated cell is phenotypically indistinguishable from surrounding cells of the same type. Further development of the initiated cell into a neoplastic cell requires a period of promotion. Under the influence of a promoter, tumor formation is accelerated through clonal expansion of initiated cells. Promoters, which do not interact directly with DNA, are a diverse group of agents believed to act by a variety of mechanisms most often resulting in increased cell proliferation. The process of promotion is considered reversible and requires prolonged and repeated exposure to promoter agents. Progression is the final step in which pre-neoplastic foci develop into malignant cells. In this stage, tumor development is characterized by karyotypic changes, increased growth rate, and invasiveness. Progression may be spontaneous, influenced by environmental factors, or mediated by progressors. Resulting tumors may be either benign or malignant.

The mechanisms of metal-induced carcinogenesis are less clear than for genotoxic agents, and they probably involve a number of biochemical events that indirectly affect the integrity of the genome of particular cells. It has been found, for example, that nickel and arsenic exposure can induce DNA hypermethylation (Tang 2000), and that arsenic inhibits DNA ligase I and II, which plays a role in DNA repair. Such non-mutational epigenetic changes could also result in suppression of tumor-suppressor genes, such as the p53 gene, triggering tumorigenesis. These “indirect” mechanisms of

carcinogenesis often translate into what are believed to be sublinear, or hockey-stick type dose–response curves. If this occurs, extrapolations from high-dose effects are likely to overpredict risks at low doses (Rudel et al. 1996).

Background tumor formation is a normal observation in control animals from rodent carcinogenicity studies. The incidence of spontaneous tumors varies between tissues, and the susceptibility of a given tissue or organ varies between species and strain, and can be influenced by other factors including diet. For example, it has been found, in lifetime studies, that the incidence of testicular interstitial cell adenoma is 49% in F-344 rats compared with 9% among FBNF1 rats (Haseman et al. 1998). A 40% food restriction lowered incidences in these strains to 19 and 4%, respectively.

24.3.3.2 Non-Cancer Effects

The non-cancer end points are subdivided into acute or chronic exposures and effects with different levels of further organization relating to the target tissue, organ, or system, depending on the risk management need.

The critical biological target is identified from an exhaustive search of published and unpublished literature until a reliable study shows an effect that occurs at doses below those causing any other measured effect. As these studies are typically done on laboratory animals, the most sensitive species and sex is used as the basis for identifying the critical dose.

One organizational scheme for target organ systems is shown in Table 24.3.

Generally speaking, the fewer the categories of classification, the more conservative or public health protective an assessment of the impacts of a mixture of chemicals.

24.3.4 Identifying Thresholds

The highest experimental “no observed adverse effect” level (NOAEL) is the basis for most practical thresholds of toxicological effects. The critical NOAEL is combined with uncertainty factors (UFs) to provide a margin of safety for the exposed population.

Acceptable Daily Intake/Air Quality Standard/
Water Quality Standard/ etc.

$$= \text{Experimental NOAEL} \div \text{Margin of Safety}$$

or:

$$\text{NOAEL} \div (\text{UF}_A * \text{UF}_H * \text{UF}_T * \text{UF}_D * \text{UF}_L)$$

Table 24.3 Target organs, tissues, or systems used by California Environmental Protection Agency for air toxicology non-cancer risk assessments

| |
|---|
| Eyes |
| Lung (upper and lower respiratory tracts) |
| Liver |
| Kidney |
| Immune system (e.g., reduced host-resistance) |
| Nervous system (peripheral and central) |
| Blood (i.e., anemia) |
| Endocrine |
| Reproductive and/or developmental |
| Gastrointestinal |
| Bones (i.e., fluorosis) |

From OEHHA (2000)

A = animal to human; H = human variability; T = temporal factors; D = data gaps/quality; and L = LOAEL* to NOAEL

UFs = 1–10, depending on source of data, with a maximum cumulative UF of 3,000 (U. S. EPA 2002). The definition of NOAELs and LOAELs (lowest observed adverse effect levels) are shown in Table 24.4.

The NOAEL concept and its implications for human health risk assessment is shown in Fig. 24.2.

An alternative to the NOAEL is the benchmark dose (BMD) approach, which is favored by regulatory agencies when the data are of sufficient quality.

Some important characteristics of the BMD are

- Benchmark doses are used by the U.S. Environmental Protection Agency (U.S. EPA) and the World Health Organization (WHO) in many non-cancer risk assessments.
- BMDs use dose–response information.
- BMDs take into account statistical uncertainty and sample sizes.
- BMDs assume a distribution of responses rather than a point estimate.
- BMDs can assume a threshold and account for background responses as options.
- Dichotomous and continuous data can be used to calculate BMDs.

A number of mathematical models exist for calculating BMDs. Public domain software developed by the U.S. EPA for benchmark dose calculations can be found at the U.S. EPA Web site (www.epa.gov).

An example of a BMD relationship is shown in Fig. 24.3. A percentage response in the test population is taken to be the practical threshold for the adverse effect. Typically this is a 5–10% response incidence.

24.3.4.1 What Is an Adverse Effect?

Not all biological responses to a toxicant are considered adverse. Some effects are considered to be adaptive responses that have no short- or long-term consequences. This gray area in the definition of a threshold for adverse effects is one of considerable discussion and debate in regulatory toxicology. Table 24.4 illustrates the types of definitions that have been assigned as severity qualifiers to adverse effects by the U.S. EPA.

Adverse effects from human clinical and epidemiological studies have also been defined in the context of regulatory purposes (Table 24.5).

24.3.5 Variation in Effects: Genetic and Phenotypic Variability in Susceptibility

The variability in response to a chemical agent can create difficulties in establishing statistically significant associations in epidemiology. However, the variability in a given response often has biological roots that are increasingly important as regulatory and public health agencies try to determine ways to identify and protect the most sensitive individuals in society from adverse toxicological effects.

Toxicological risk assessment has traditionally relied on estimates of no-effect thresholds (i.e., NOAELs) combined with uncertainty factors, which are intended to account for the fact that individual variability in response exists. Default values between 1 and 10 are typically used in these calculations because the precise amount of individual variability is not known.

More recently, investigators have been determining the degree of variability in physiological parameters. For example, the U.S. National Research Council (NRC) reports a range of elimination half-lives for 13 different drugs that are 0.7- to 17-fold greater in newborn infants than in adults (NRC 1993). For a given rate of exposure, these drugs would remain for a longer time in an infant's body, thus likely increasing the infant's susceptibility.

The individual variability in some key toxicokinetic mechanisms have been described using clinical and epidemiological studies as shown in Table 24.6.

Table 24.6 shows that although toxicological risk assessment relies on the assumption that a ten-fold uncertainty factor for individual variability is health protective, in some cases clearly a factor of 10 comes nowhere near the amount of variability that actually exists. However, this type of research with application to risk assessment is relatively recent, and more data are needed in order to more precisely define what are appropriate default values for this parameter.

Although the long neglected field of human susceptibility to environmental toxicants is currently receiving renewed

Table 24.4 U.S. EPA—Interim guidelines for development of inhalation reference concentrations^a

| Effect or no effect level | Rank | General effect | Cal/EPA severity ranking |
|---------------------------|------|--|--------------------------|
| NOEL | 0 | No observed effects | <Mild |
| NOAEL | 1 | Enzyme induction or other biochemical changes, consistent with possible mechanism of action, with no pathologic changes and no change in organ weights | <Mild |
| NOAEL | 2 | Enzyme induction and subcellular proliferation or other changes in organelles, consistent with possible mechanism of action, but no other apparent effects | <Mild |
| NOAEL | 3 | Hyperplasia, hypertrophy, or atrophy, but no change in organ weights | ≤Mild |
| NOAEL/LOAEL | 4 | Hyperplasia, hypertrophy, or atrophy, with changes in organ weights | Mild |
| LOAEL | 5 | Reversible cellular changes including cloudy swelling, hydropic change, or fatty changes | Mild/severe |
| (LO)AEL ^b | 6 | Degenerative or necrotic tissue changes with no apparent decrement in organ function | Severe |
| (LO)AEL/FEL | 7 | Reversible slight changes in organ function | Severe |
| FEL | 8 | Pathological changes with definite organ dysfunction that are unlikely to be fully reversible | Severe |
| FEL | 9 | Pronounced pathologic changes with severe organ dysfunction with long-term sequelae | Severe |
| FEL | 10 | Death or pronounced life-shortening | Life-threatening |

^aAdapted from Hartung (1987)

^bThe parentheses around the LO in the acronym LOAEL refer to the fact that any study may have a series of doses that evoke toxic effects of rank 5–7. All such doses are referred to as adverse effect levels (AELs). The lowest AEL is the (LO)AEL

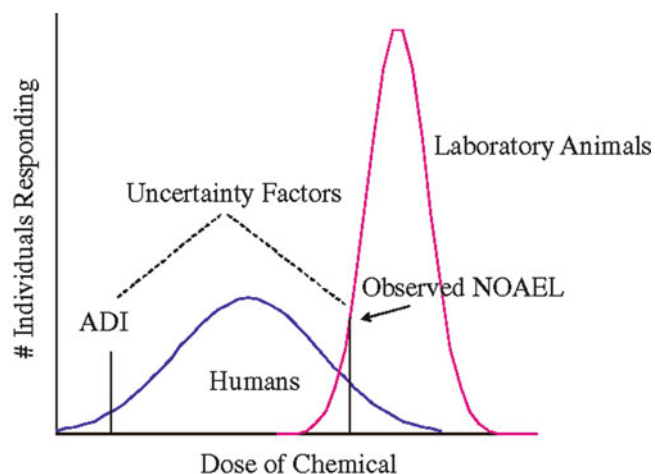


Fig. 24.2 Concept of extrapolation from animal experimental NOAEL to humans in deriving an acceptable daily intake (ADI). The laboratory animals are assumed to be, on average, less sensitive to the toxicant than humans, and are also assumed to have less individual variability (indicated by the relatively narrow distribution on the right)

attention, there is only scant literature on factors influencing susceptibility to heavy metals (Gochfeld 1997).

24.4 Toxicology and Epidemiology: How Is Environmental Medicine Studied?

Toxicology, risk assessment, and epidemiology all have important roles in the study of environmental medicine. The scientific confidence in the public health actions that are taken in response to environmental contaminants is a function of how thoroughly each of these areas are

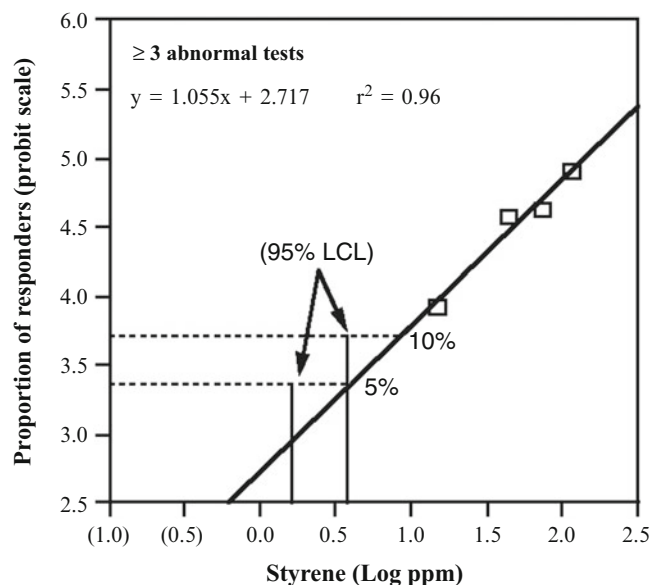


Fig. 24.3 Benchmark dose effect of styrene on neurobehavioral tests in plastics workers. (Data from Mutti et al. 1984; Rabovsky et al. 2001.) LCL is the statistical 95% lower confidence limit on the probit line

addressed. History shows that heavy emphasis on one discipline alone can lead to actions that later are determined to be unfounded. The case of saccharin is one example. Saccharin was, for many years, considered to be a probable human carcinogen by the IARC and the U.S. National Toxicology Program due to its ability to induce bladder cancer in male rats. Many studies were done on rats to confirm this effect, and a dose–response relationship was developed and widely accepted. At one point, saccharin was one of the most studied compounds in terms of long-term cancer bioassays

Table 24.5 California environmental protection agency symptom and sign severity rating for human studies

| Severity rating | Symptoms | Signs/laboratory findings |
|------------------|--|---|
| Mild adverse | Mild subjective complaints with few to no objective findings: | Statistically significant findings of pre-clinical significance: |
| | Mild mucous membrane (eye, nose, throat) irritation | Mild conjunctivitis |
| | Mild skin irritation | Mild lung function changes |
| | Mild headache, dizziness, nausea | Abnormal immunotoxicity test results |
| | | Mild decreases in hemoglobin concentration |
| Severe adverse | Potentially disabling effects that affect one's judgement and ability to take protective actions; prolonged exposure may result in irreversible effects: | Clinically significant findings: Findings consistent with central or peripheral nervous system toxicity |
| | | Loss of consciousness |
| | | Hemolysis |
| | Severe mucous membrane irritation | Asthma exacerbation |
| | Blurry vision | "Mild" pulmonary edema |
| | Shortness of breath, wheezing | Clinically significant lung function changes |
| | Severe nausea | Cardiac ischemia |
| | Severe headache | Some cardiac arrhythmias (e.g., atrial fibrillation) |
| | Incoordination | Renal insufficiency |
| | Drowsiness | Hepatitis |
| Life-threatening | Panic, confusion | Reproductive/developmental end points (e.g., infertility, spontaneous abortion, congenital anomalies) |
| | | Potentially lethal effects: |
| | | Severe pulmonary edema |
| | | Respiratory arrest |
| | | Ventricular arrhythmias |
| | | Cardiac arrest |

Table 24.6 Reported ranges of variability in parameters related to susceptibility

| Parameter | Width of 90% range for an average chemical or test |
|--|--|
| Systemic uptake pharmacokinetics | |
| Breathing rates | 1.8- to 2.8-fold |
| Half-life or elimination | 2.3- to 5.8-fold |
| Skin absorption | 2.5-fold |
| Maximum blood concentration | 2.3- to 11-fold |
| Area under concentration curve | 3.0- to 8.1-fold |
| Blood concentration measurements | |
| Serum PCB concentrations | 12-fold |
| Blood mercury levels | 12-fold |
| Blood lead levels | 13-fold |
| Pharmacodynamic or combined kinetic and dynamic parameters | |
| Cisplatin hearing loss | 4.1-fold |
| Effects of methyl mercury in adults | 12- to 78-fold |
| Fetal/developmental effects of methylmercury | 460- to 10,000-fold |
| Hemodynamic responses to nitrendipine | 8.3- to 17-fold |
| FEV1 response to cigarette smoke | 8.3-fold |
| Salbutamol FEV1 increase (asthma) | 128-fold |
| Acute toxicity | |
| Death from compounds metabolized by plasma cholinesterase | 5.5-fold |
| Death from parathion | 12-fold |

Adapted from Hattis (1996)

and dollars spent. This carcinogen designation was then driven by toxicity testing because the mechanism for cancer formation from saccharin was not known, nor was it known

why only male rats were susceptible, and not mice, any other species, or female rats (see also Chaps. 22 and 25, this volume).

Table 24.7 Basic framework for the identification, risk assessment, and epidemiological study of environmental contaminants

| Discipline/Area of research | Goals and outcomes |
|--|--|
| Basic biochemical toxicological research | Identification of biochemical mechanisms |
| | Hypothesis of downstream physiological end points |
| | Development of biomarkers |
| Toxicity testing | Descriptive toxicology test battery (acute, chronic, mutagenicity, carcinogenicity, reproductive/developmental toxicity, sensitization) |
| | Identification of critical effects starting from high doses and reducing dose until no effect is seen |
| | Establishment of dose-response relationship |
| | Multiple species and both genders |
| Risk assessment and management | Identification of a critical dose (no observed effect level or benchmark dose) |
| | Application of margin of safety (uncertainty factors) |
| | Establishment of an acceptable chronic dose level |
| Epidemiological research | Probe established toxicological limits and biochemical mechanisms determined from animal studies to determine if they are applicable to humans |
| | Describe the probabilities of adverse effects in humans occurring following exposure |
| | Signal for further mechanistic research or the need to develop human biomarkers for exposure or effect |

The epidemiology research showed that there was no evidence for elevated incidence of cancers in humans using saccharin, but there were concerns that the latency period required for cancer to develop in people had not been allowed to mature. The mechanism of cancer formation was later found to be due to induction of a male-rat-specific protein (alpha-2U globulin) that caused chronic irritation of the bladder, which led to bladder cancer at high doses (Turner et al. 2001). This led regulatory agencies to de-list saccharin as a human carcinogen in 1999 (IARC 1999). The relationship of these disciplines in environmental medicine is shown in Table 24.7.

24.4.1 Concepts of Dose and Duration

24.4.1.1 Cancer Potency

Chemicals that are carcinogenic to humans are identified through several authoritative bodies using established weight of evidence approaches. The IARC, the U.S. National Toxicology Program (NTP), and the U.S. EPA are the three most authoritative sources for identification of new and existing carcinogens.

There are 48 individual chemicals that are known human carcinogens under the IARC classification scheme.

The data from cancer bioassays is usually fit to a linearized multistage model, which is of the form originally described by Crump (1984).

$$\text{Linearised multistage model: } P(d) = 1 - e^{-(q_0 + q_1 d + q_2 d^2 + \dots + q_k d^k)}$$

$$P(0) = 1 - e^{-q_0}$$

where $P(d)$ is the probability of developing a tumor at a given dose rate and $P(0)$ is the estimated background incidence. The q parameters are derived from the model.

Cancer potency is usually described by a dose-response slope factor (q_1) and its respective 95% confidence limit (q_1). The units of potency are usually in $(\text{mg/kg/day})^{-1}$ which, when combined with a given dose level, gives a unitless risk factor (e.g., 10^{-6} , or 1 in a million). This concept applies to daily doses experienced over a chronic period, up to an entire lifetime. Much less is known about estimating risks from single acute exposures to carcinogens, and there are few animal studies through which to judge the difference in the dose-response relationship.

Often, a rodent cancer bioassay yields information only at a few doses that far exceed those found in the environment, and the dose-response is extended to very low doses.

Potency factors assume the absence of a threshold for cancer at low doses. Therefore, it may be inappropriate to apply potency estimates to carcinogens that are thought to have a threshold (e.g., non-genotoxic carcinogens, such as dioxin).

The utility of cancer potency factors lies in their use in cancer risk projections. When calculating cancer risks, if exposures to specific carcinogens can be quantified, then it is assumed that the risk of getting cancer from a long-term exposure is a function of exposure (i.e., mg/kg/day) multiplied by the respective cancer potency factor $(\text{mg/kg/day})^{-1}$. The two most critical assumptions with this calculation are

1. The assumption that the basis for the cancer potency factor is a mechanism that applies to human physiology
2. The tumors seen at high doses in experimental studies are part of a linear or curvilinear function that extends to low doses that are more relevant to environmental exposures

Table 24.8 Expected variability in the abnormal responses to styrene

| Fold differences between percentiles | | | |
|---------------------------------------|---------------------------------------|----------------------------|----------------------------|
| Number of abnormal neurological tests | Probit slope (1/log GSD) ^a | (5–95% range) ^b | (1–99% range) ^b |
| ≥1 | 1.346 | 270 | 2,860 |
| ≥2 | 1.225 | 485 | 7,190 |
| ≥3 | 1.055 | 1,300 | 25,540 |

From Rabovsky et al. (2001)

^aThe probit slope was taken from the log-probit analysis using Tox-Risk V.3.5(30) described for Table 24.3

^bThe range of variability is obtained from the equation:

$$[\log(X) - \log(GM)] / \log(GSD) = t(\alpha)$$

where X is the distance on the dose axis from the mean to the 95th (or the 99th) percentile. To obtain the range of variability, the same distance from the mean to the 5th (or 1st) percentile is added to “X” and the bounds of the 5th–95th (or 1st–99th) percentile are the ranges of variability. Other abbreviations are GM, geometric mean; GSD, geometric standard deviation; and t (α), t distribution value at the desired test level (i.e., 0.05 or 0.01)

The California Environmental Protection Agency (Cal/EPA) has an active program that identifies carcinogens and lists potency values for each on its Web site (www.oehha.ca.gov).

24.4.1.2 Dose–Response Slope

The slope of the response curve from a toxicology study imparts significant meaning to the causal relationship of the chemical and effect being studied. The dose–response relationship also helps in understanding the risks from exposure to low doses.

Some additional uses of the dose–response relationship include the characterization of individual variability in the measured response to the chemical. Table 24.8 shows the relationship of probit slope term to the individual variability in a battery of neurological tests in response to styrene exposure in the workplace (Rabovsky et al. 2001). In general, the more shallow the dose–response slope, the greater the variability in the test population. When using a log-normal model to describe a dose–response relationship, slope terms that approach 1.0 show very large individual variability (Table 24.8).

24.4.2 Estimating Exposure (Analytical Chemistry, Biomarkers, and Modeling)

Exposures to metals can be measured or estimated in various ways. For chronic dietary exposures, blood samples for the metal may be the most direct and simple measure of exposure. For historical exposures, blood samples may not be appropriate if the body has had time to depurate the metal from the bloodstream. Lead has a half-life of about 25 days in the blood. Methylmercury has a half-life for elimination from the body of about 50 days in adult males and females. However, infants have poor elimination of organic and inorganic heavy metals in the first 6 months prior to development of metal transport systems. It is possible that mercury is eliminated much more slowly in the child. Cadmium is

removed from the human body much more slowly, so that the elimination half-life is on the order of 20 years (Gochfeld and Syers 2001).

Metallothioneins (MTs) are metal-binding proteins that are considered central in the intracellular regulation of metals such as copper, zinc, and cadmium. Variability in tissue MT levels influence susceptibility of tissues and species to the toxic effects of some metals, such as cadmium and mercury.

Metallothionein is the major protein thiol induced in cells exposed to cytokines and bacterial products (Schwarz et al. 1995). This protein is inducible by exposure to some metals, and it appears to impart protection from some adverse effects. For example, zinc exposure during fetal life results in MT induction (Mengheri et al. 1993). Zinc pretreatment lowers cadmium carcinogenicity in laboratory animals presumably through induction of MT (Coogan et al. 1992). Induction of MT protects against cadmium toxicity in rats (Singh and Rana 2002). Similarly, MT is thought to contribute to the placental barrier to the transfer of mercury to the fetus (Yamamoto et al. 2001).

24.4.3 Is There a Health Effect? Animal Models

The widespread use of animal models in toxicity testing continually raises the possibility that a given adverse effect may not be relevant to humans, or that the animal model studied may substantially underpredict human risk. The case of saccharin already described, is an example of the former. The converse of the saccharin case, however, can also be true. Arsenic, for example, is a human carcinogen and a human neurotoxin, but it does not appear to cause cancer in laboratory animals at doses that are considered carcinogenic to humans. Thalidomide is a prominent case in which a relatively minor heart valve developmental defect in rodents translated into major deformities in human babies. Benzene is another example where humans appear to be the most sensitive species tested for its critical effect (leukemia).

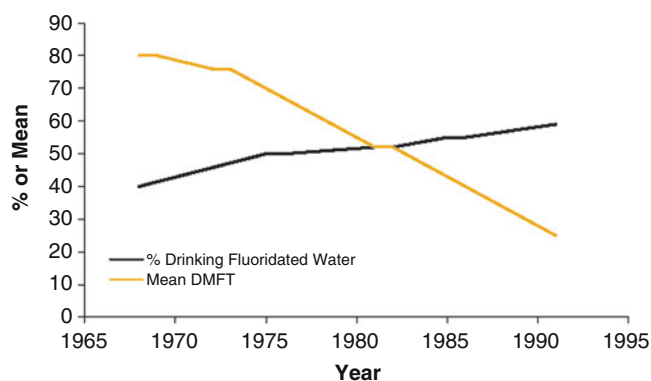


Fig. 24.4 Percentage of population residing in areas with fluoridated community water systems and mean number of decayed, missing (because of caries), or filled permanent teeth (DMFT) among children aged 12 years, United States 1967–1992. (From National Center for Health Statistics 1974, 1981; National Institute of Dental Research 1989; CDC unpublished data, 1988–1994)

Thus, animal models show a number of examples of failure in predicting effects on humans. However, by and large, animal models, particularly when multiple species are tested, are thought to provide adequate evidence for an initial risk assessment of a substance to proceed, provided that adequate margins of safety are used. Epidemiological studies will always be needed to ascertain if the safe limits proposed in risk assessment are adequately protective.

In the case of arsenic, there is significant interspecies variability in metabolism. However, in most mammals, arsenic is metabolized and detoxified by the addition of methyl groups, and is eventually excreted, primarily in urine, in a mono- or dimethylated form. The methylation pathway is dependent on folate metabolism, which provides methyl groups through conversion of S-adenosylmethionine to S-adenosylhomocysteine. The availability of methyl groups from this pathway is thus essential to the metabolic detoxification of arsenic and may at least partially account for both inter- and intraspecies differences in sensitivity to this toxicant. Human serum, for example, is folate-deficient compared to rodent serum (unpublished observation), and this observation may explain experimental findings that arsenic, a known carcinogen in humans, does not induce cancer in rodents.

Given the critical role of methylation in the disposition of arsenic, further characterization of the enzymatic basis of arsenic methylation is required. To date, human arsenic methyltransferase has not been isolated, but transferases are generally polymorphic. Understanding the factors affecting human sensitivity would improve the arsenic risk assessment. The objective of this section is to evaluate variations in arsenic metabolism as reflected in variations in urinary metabolites or other biomarkers of exposure as associated with the exposure level, nutritional status, genetic factors, and other variables. Included in this area are studies to

improve mass balance data on typical human metabolism of arsenic at various doses and chemical forms. There is a need for the development and refinement of assay procedures to characterize arsenic methyltransferases in human tissues. In addition, these studies would compare biomarkers of arsenic metabolism in individuals exposed to varying levels of arsenic with differences that include, but are not limited to, nutritional status, age, sex, and genetic variations.

24.4.4 Evidence at the Population Level

Further evidence (follows from animal studies section) of the relationship between an exposure and a health effect can be sought through the epidemiological study of human populations. Such epidemiological studies take three main forms: cross-sectional, case-control, and cohort. Each study design has its own strengths and weaknesses, and *all answer different questions*.

The cross-sectional study is in essence a survey to determine how common something is, or at what level it occurs. In Fig. 24.4, for example, the prevalence of caries in the teeth of children was determined by cross-sectional survey. By carrying out such surveys in populations using different drinking water supplies, it was possible to answer the question: Are caries more common in populations with low fluoride exposure? An advantage of the cross-sectional study is that it is relatively quick, easy, and cheap to administer. Disadvantages include that it cannot take into account individual exposures and is subject to confounding. For example, if the people drinking low-fluoride water are also poorer, they may have more caries for dietary reasons.

The case-control study starts with identified cases of a disease and compares their exposure to controls who do not have the disease. In the case study on amoebic meningitis in Sect. 22.2, for example, children with the disease would be identified, and the frequency of their hot spring usage would be compared to that of children without the disease. With such a study it is possible to answer the question: Did children with amoebic meningitis swim in hot springs more frequently than children without amoebic meningitis? If yes, then hot springs are implicated by association, but note that this does not demonstrate a causal relationship.

An advantage of the case-control study is that risk factors for very rare events can be identified. A disadvantage is that they contain no denominator information: note that we have no idea how many children swam in the hot springs to give rise to the few rare cases that we are studying, and we therefore cannot say how dangerous that activity is.

The cohort study, seen by many as the epidemiological gold standard, starts with a group of people with a common exposure.

The risk factors of cases with the disease are then compared to the risk factors of controls without the disease, all still within this group or cohort of people. For example, a cohort might be defined as all people living in a village with high levels of arsenic in the water supply. Some of these people would develop skin cancer and become “cases,” whereas others would not develop skin cancer and would instead become “controls.” The epidemiologist would record the water consumption habits of all members of the cohort. With such a study it is possible to ask the question: Do people who drink more water develop skin cancer more frequently? If yes, the arsenic-rich water would be implicated by association, but again, a causal relationship has not been established. The advantage of this study design is that it does provide denominator information, and it is therefore possible to directly calculate the risk of developing cancer from drinking the water. The disadvantage is that this approach is both very time-consuming and potentially very expensive as very large cohorts are often required to give the study enough power to achieve statistical significance.

As mentioned, all of these studies are epidemiological, and can at best establish association between exposure and effect. To establish a causal relationship between an exposure and a health effect, several other criteria are generally considered, including the following (Hill 1965): a temporal relationship between exposure and effect; a biologically plausible relationship, including a dose–response effect; associations by epidemiological studies that are both strong and consistent; and reversibility of the association if the exposure is removed.

A number of approaches to the study of environmental medicine have been outlined in this chapter. Let’s not forget that the aim of such a study is to devise interventions to reduce morbidity and mortality, which is the subject of the following section.

24.5 Health Protection: How Can Adverse Effects Be Minimized?

In Sect. 22.2 (and Table 24.1) we explored a useful framework for considering health effects from environmental exposures. Other than simply to satisfy the human compulsion to classify things, such a framework is a prerequisite to health protection: in order to minimize the adverse health effects of environmental exposure, we must first be able to consider all possible exposures. We can then prioritize surveillance and intervention so as to maximize health gain from the use of our (invariably limited) resources.

24.5.1 Risk Assessment

One common approach to risk assessment follows the four simple steps of hazard description, dose–response estimation, exposure assessment, and risk characterization. These can be simply illustrated here using an example such as exposure to volcanic gases during an eruption (see Chap. 10, *Volcanic Emissions and Health*, this volume). The hazard description would list the gases concerned, e.g., CO₂, H₂S, and HF, and detail the volume, concentration, and duration of emission. The dose–response estimation (effect) would consider, usually graphically, the relationship between the amount of gas and the relevant health effect. Thus respiratory distress may increase in a linear fashion with the dose of gas inhaled, and a threshold may exist at which consciousness is lost.

The exposure assessment would take into account how many people are likely to suffer from such health effects, for how long, and if any particular groups are at greater risk. For example, the number of people living in a village downwind from the eruption will be relevant, as will be the number of children in cots (arguably more susceptible to suffocation from gas that is heavier than air).

The risk characterization summarizes all this information into a prediction about the likely outcome if the hazard goes unchecked. For example, 2 deaths in children and 100 adults with respiratory distress may be predicted for such a village if it is not evacuated. Medical and civil defense authorities will then make a decision about the appropriate deployment of resources based on this risk assessment. Should the two buses available be deployed to evacuate this village, or would they be better deployed to evacuate the village on the other side of the mountain that is potentially in the path of a lava flow?

The problem is that even with the best risk assessment, there is always a degree of uncertainty, and decisions about intervention can therefore be difficult to make. It seemed sensible at one time to recommend that well water be used in Bangladesh to avoid the risk of gastrointestinal disease from pathogens in surface waters. The well water, however, turned out to contain arsenic at levels that were not anticipated (see Chap. 12, *Arsenic in Groundwater and the Environment*, this volume). It is sometimes unclear if a known exposure constitutes a health risk or not. For example, low-level chronic exposure to geothermal hydrogen sulfide has not been demonstrated to cause clear-cut pathology, but one might expect it to on the basis of respiratory and neurological toxicity at higher levels of exposure. In such cases, practitioners of environmental medicine often apply the “precautionary principle,” which states that any substance suspected of adversely affecting health should be avoided (as far as possible) until proven otherwise.

24.5.2 Surveillance

Surveillance is the term used, in environmental medicine, to refer to the ongoing monitoring processes that inform public health intervention. Surveillance is the use of monitoring data to attempt to reduce morbidity and mortality: without the completion of this criterion, surveillance would be no more than data collection.

A good example of a surveillance system is the “notifiable disease” list, which compels medical practitioners in most countries to notify some authority responsible for disease control on each occasion that he makes a diagnosis of one of the diseases on the list. Lead poisoning causes learning difficulties and neurological complications, and is on the notifiable list in most countries. The relevant authority collects and analyzes the notified case data to determine the source of the exposure; for example, toddlers are commonly poisoned by ingesting flakes of old lead-based paint in poorly maintained houses, and adults may have occupational exposure in industries such as battery recycling.

The “surveillance loop” is completed when this information is used to impose recommendations for home improvement or factory practices. Note that the frequency of notified cases provides feedback as to the effectiveness of the interventions (at least on a regional or national scale), thereby forming a genuine “intelligence loop.”

In the example above, health surveillance was carried out for the health effects of exposure to the element lead. It is also possible to carry out *hazard* surveillance, where the environmental levels of, e.g., lead are monitored directly, rather than (or as well as) monitoring the health effects caused by lead. The same requirements for surveillance hold, and the data on lead concentration and distribution are used to inform public health intervention: the lead level in the factory can now be kept below safety limits without the need for workers to develop symptomatic disease (which is obviously preferable). The implementation of one or both types of surveillance, health and hazard, are integral to the practice of environmental medicine. In conjunction with the environmental medicine framework discussed in Sect. 22.2, it should now be possible for the reader to devise, at least at the theoretical level, surveillance systems to deal with most situations that might be encountered in medical geology.

24.5.3 Intervention

24.5.3.1 Intervention Success Story: The Fluoridation of Public Water Supplies

In the 1930s American dental epidemiologists noted a considerable regional variation in the rate of dental caries. By carrying out a cross-sectional study (as described in Sect. 24.4.4), Dean (1936) established an association

between differing levels of fluoride (F^-) in regional water supplies and caries rates in the populations drinking those waters. Although fluoride is a toxin that in high concentration can kill, it appeared in this case that a small amount in the drinking water was beneficial to dental health. In populations supplied with drinking water containing about 1 mg/L F^- , dental caries rates were reduced by about 50%. The variation in fluoride levels in drinking waters in those days was entirely natural, and resulted from the dissolution of fluorine by surface waters as they coursed over fluorine-rich substrates such as geological deposits of marine origin. Population health was therefore directly affected by living in an area with particular geological characteristics, a situation that is in essence the theme of this book.

Public health authorities now began to ask the obvious question: For populations not living in fluoride-rich areas, could dental health be improved by artificially supplementing F^- levels in drinking water? The suggestion was examined from several perspectives including cost-benefit considerations and human health risk assessment (Sect. 24.5.1). The risk was (and remains) one of balancing the fluoride delivery carefully so as to achieve the reduction in caries rate without also causing fluorosis—the condition of excessive chronic fluoride ingestion. Many middle-aged people in the western world have dental fluorosis (stained patches of brittle enamel) from receiving both fluoridated water and fluoride tablets as children. Industrial fluorosis is also known, largely historically, as an occupational hazard in the aluminum and fertilizer industries. In these cases, fluoride deposition into bone increases bone and cartilage density which can result in restricted flexibility and movement, especially around the lumbar spine (Derryberry et al. 1963). In the developing world, many people in specific geographic areas have a far more serious form of fluorosis, which is known as endemic fluorosis. This is a potentially crippling disease, the major manifestation of which is the overgrowth and distortion of bone, with tendinous, articular, and neurological involvement. Such severe disease only results after many decades of ingestion of drinking water with 10 mg/L F^- or more, a concentration one order of magnitude higher than the 1 mg/L observed to be beneficial by Dean (1936). Since the 1950s therefore, public drinking water supplies in most developed countries have been topped up to about 1 mg/L of F^- , with minor adjustments to account for differing levels of climate-dependent water consumption. The improvement in the dental health of children has been remarkable since that time, with large reductions in caries rates.

The debate continues to this day about the relative contribution of water fluoridation to this reduction in dental caries rates, because there have been concurrent improvements in nutrition, dental hygiene, and dental services that also contribute to a reduction in the incidence of caries. The issue has become further blurred by the advent of fluoridated

toothpaste, sports drinks, and other sources of fluoride that dilute the improvement attributed to fluoridated water alone. It is known, however, that populations receiving fluoridated drinking water show better dental health, on average, than do control populations without fluoridated water (WHO 1994). Health surveillance data (caries rates) collected by school dental services show that this continues to be the case, and hazard surveillance data (water F^- levels) collected by water treatment plants continue to ensure that populations are not at risk of fluorosis. The fluoridation of public water supplies is therefore a good example of a successful public health intervention informed by ongoing surveillance.

24.6 Case Study: Arsenic

24.6.1 Exposure to Arsenic

Arsenic is a metalloid element found ubiquitously in nature. It is present in the Earth's crust with an average concentration of 2 mg/kg. Arsenic can be found in soil, air, water, food, and some manufactured chemicals. Humans can be exposed to arsenic from either natural sources or anthropogenic sources. Natural sources of arsenic include rocks (soil), volcanic emissions, undersea smokers, and extraterrestrial material. Volcanic emission is the most important natural source of arsenic. Arsenic can be found in more than 200 mineral species, of which the most common is arsenopyrite. Anthropogenically, arsenic can be found in products of herbicides, fertilizers, pesticides, leather treatment, cotton desiccants, wood preservation, animal feeds as food additives, and pharmaceuticals (see also Chaps. 12 and 25, this volume).

Humans can be exposed to arsenic through ingestion of arsenic-containing water, food, and drugs (such as Fowler's solution containing 1% of potassium arsenite used to treat psoriasis and arsenic trioxide used to treat leukemia). Airborne arsenic can be absorbed into the bloodstream in workers involved in the processing of copper, gold, and lead ores; in the production and use of arsenic-containing pesticides; in the manufacturing of glass, semi-conductors, and pharmaceutical substances; in using arsenic as pigments and dyes; in burning coal containing high levels of arsenic (Guizhou Province, China); in smoking high-arsenic-contaminated tobacco; and in chimney sweeping.

Water contamination is the most common source of arsenic exposure. Currently, Bangladesh and West Bengal, India, have the most serious problem of groundwater contamination with arsenic in the world. Tracing back the history of these areas, surface water was replaced by tubewell water in 30 years ago to fight against infectious diarrheal diseases. These programs to provide "safe" drinking water from

underground unexpectedly brought up another health problem of arsenic hazards. It is estimated that more than 95% of the 120 million people in Bangladesh drink tubewell water and more than one-third of the tubewell water contains arsenic above 0.05 mg/L (the maximum allowable level recommended by the WHO). In 2001 the U. S. EPA lowered the maximum allowable level of arsenic in drinking water from 0.05 mg/L to 0.01 mg/L. High arsenic level in drinking water is also reported in countries such as Argentina, Australia, Chile, China, Hungary, Mexico, Peru, Taiwan, Thailand, and the United States. See *Arsenic in Groundwater and the Environment* (Chap. 12), this volume.

24.6.2 Effects of Arsenic

Arsenic exists in four valence states: -3 , 0 , $+3$, and $+5$. Elemental arsenic and arsine (-3) exist in strongly reducing environments; arsenite ($+3$) is the dominant form in moderately reducing conditions; and arsenate ($+5$) is stable in oxygenated environments. Inorganic forms of arsenic are much more toxic than organic forms found abundant in seafoods, and, in general, inorganic arsenic of trivalent forms are more toxic than pentavalent forms. Immediate symptoms of an acute poisoning typically include vomiting, esophageal and abdominal pain, and bloody "rice water" diarrhea. However, a variety of symptoms and signs involving the gastrointestinal, dermal, nervous, renal, hepatic, hematopoietic, cardiovascular, respiratory, and ophthalmic systems can be observed (Table 24.9) (Chen et al. 1999; Tseng 1999). Treatment with chelating agents such as dimercaprol or dimercaptosuccinic acid during acute intoxication is classical but may have varying effects. Chelating agents may not be effective in chronic poisoning. See *Biological Responses of Elements*, this volume.

Long-term exposure to arsenic can cause a variety of cancers involving the skin (squamous cell and basal cell carcinoma), lung, bladder, kidney, and liver. Although arsenic does not induce point mutations, it can cause chromosomal aberrations, affect methylation and repair of DNA, induce cell proliferation, transform cells, and promote tumors.

A wide spectrum of non-cancerous diseases and clinical problems are also reported in long-term arsenic exposure (Table 24.9). Arsenic skin lesions are characterized by the coexistence of hyper- and hypopigmentation giving rise to a raindrop pattern (Fig. 24.5) and hyperkeratosis of the palms and soles (Fig. 24.6). In recent years, long-term exposure to arsenic from drinking water has also been found to be highly associated with hypertension and diabetes mellitus (Tseng et al. 2000, 2002). Preclinical microcirculatory defects (Tseng et al. 1995) and arterial insufficiency (Tseng et al. 1994) can also been demonstrated in subjects exposed to arsenic. Arsenic could also cause lower IQs in children

Table 24.9 Non-cancerous effects of arsenic on humans

| Organ system | Diseases or symptoms/signs |
|------------------|---|
| Dermal | Hypo- and hyperpigmentation (raindrop pattern), hyperkeratosis of palms and soles, exfoliative dermatitis, Bowen's disease (pre-cancerous lesions), facial edema, non-pitting pedal edema |
| Cardiovascular | Arrhythmia, pericarditis, ischemic heart disease, peripheral vascular disease, cerebral infarction, hypertension, microcirculatory defects |
| Gastrointestinal | Abdominal discomfort, anorexia, malabsorption, body weight loss |
| Nervous | Peripheral neuropathy involving sensory and motor systems, cranial nerve involvement, hearing loss, mental retardation, encephalopathy |
| Renal | Nephritis and proteinuria |
| Hepatic | Fatty degeneration, non-cirrhotic portal fibrosis, cirrhosis, hepatomegaly |
| Hematopoietic | Bone marrow hypoplasia, aplastic anemia, leukopenia, thrombocytopenia impaired folate metabolism, karyorrhexis |
| Respiratory | Rhino-pharyngo-laryngitis, tracheobronchitis, pulmonary insufficiency (emphysematous lesions) |
| Ophthalmic | Conjunctivitis |
| Reproductive | High perinatal mortality, low birth weight, spontaneous abortions, stillbirths, pre-eclampsia, congenital malformation |
| Metabolic | Diabetes mellitus, goiter |

**Fig. 24.5** Raindrop pattern of hyper- and hypopigmented skin lesions in a patient with long-term arsenic intoxication**Fig. 24.6** Hyperkeratosis of the sole in a patient with long-term arsenic intoxication

exposed to arsenic in Thailand. The symptoms and signs that arsenic causes appear to differ between individuals, population groups, and geographic areas.

24.6.3 The Study of Arsenic Intoxication: The Example of Blackfoot Disease

Exposure to arsenic from drinking water in Taiwan has been shown to cause a severe peripheral vascular disease, which might progress from intermittent claudication, ulceration, gangrene, and spontaneous or surgical amputation (a case with spontaneous amputation is shown in Fig. 24.7). The disease has been named blackfoot disease after its clinical appearance (Tseng 1999, 2002). This disease was first reported in the early twentieth century and was confined to the southwestern coast of Taiwan where people used artesian well water from as deep as 100–300 m underground (Tseng et al. 1996). The prevalence ranged from 6.51 to 18.85 per 1,000 people in different villages. A series of epidemiologic studies and surveillance of the arsenic concentrations of the artesian wells carried out during the mid-twentieth century revealed the association between blackfoot disease and the consumption of high-arsenic-containing artesian well water. Besides arsenic intake from well water, residents in the endemic area could also be exposed to arsenic from a variety of other sources, because the artesian well water was extensively used for agricultural and piscicultural purposes. The amount of arsenic ingested by the residents of the endemic area was estimated to be as high as 1 mg per day. The lethal dose in humans is estimated to be 1 mg/kg/day.

Although studies in several other countries have demonstrated that arsenic exposure can be associated with some forms of peripheral vascular disease, similar endemic occurrence of severe blackfoot disease has not been observed. It is possible that nutritional status, coexistence of other factors, and interaction with other trace elements determine the development of the various clinical manifestations.

There are two main pathways of arsenic metabolism: the reduction reactions and the oxidative methylation reactions.



Fig. 24.7 Spontaneous amputation of the third toe in the right foot of a subject living in the blackfoot disease endemic area in Taiwan

Pentavalent arsenic is reduced to trivalent arsenic, followed by the methylation reactions to form mono-, di-, and trimethylated products. S-adenosyl methionine is the methyl donor and glutathione is an essential cofactor. Low amounts of methionine or protein in the diet decrease the methylation of inorganic arsenic in animals and similar nutritional deficiency was observed in the residents of blackfoot disease areas. Vitamin B₁₂ is needed in the methylation process and insufficient intake of this vitamin in poor people and/or increased requirement during the reproduction ages in the women may put these people at higher risk for the development of arsenic-related health problems. Zinc and selenium may provide protective effects against the toxic effects of arsenic, and residents in the blackfoot disease areas were found to have deficiency of these elements in their diet. Lower levels of beta-carotene have also been shown to carry a higher risk of developing vascular disease and skin cancers in residents of the blackfoot disease endemic areas (Hsueh et al. 1997, 1998).

The absorption, distribution, and metabolism of arsenic differ significantly across species. Animals are less sensitive to the toxic effect of arsenic and most of the effects of long-term arsenic exposure on humans are not observed in animals. Genetic factors may play important roles on these metabolic cascades of arsenic; and thus, may also be involved in the development of the clinical effects of arsenic.

24.6.4 Public Health Intervention

The arsenic-related health problems in emerging endemic areas can be critical issues in public health. Drinking water poses the greatest threat to public health from arsenic. However, exposure from coal-burning, working environment, mining, and industrial emissions may also be significant in some areas. There is no universal definition of the disease caused by arsenic and there is no way to differentiate pathologically those vascular or cancerous lesions caused by arsenic from other etiologies. All of these complicate the assessment of the burden of arsenic on health. However, the use of interventional measures to terminate the hazards associated with arsenic should not wait until all these ambiguities are clarified. Up to now, there is no magic bullet for the treatment of the diseases associated with arsenic intoxication. The best strategy is prevention and avoidance of exposure. New sources of water and coal with low arsenic contents, techniques for arsenic removal from drinking water, decreasing industrial arsenic emissions, improving working environments, and promoting health education among the affected people are necessary.

As for the conditions in Bangladesh, a collaborative approach is required for scientists, health workers, policy makers, and members of the community to work together to plan and implement a sustainable and environmentally friendly water supply system. The government and professional people should have reliable, timely, and easily available information on the status of knowledge about the problems and what can be done to tackle the problems. Large-scale and concerted action is required from all sectors to take effective and practical remedial measures at affordable cost.

People need to be educated with correct knowledge about arsenic. Arsenic-related health problems are not infectious and they are manageable with a change of water-consumption pattern and adequate intake of food nutrients. Absorption of arsenic through the skin is minimal and thus hand-washing, bathing, laundry, etc., with water containing arsenic do not pose significant risk. However, arsenic-containing water is readily absorbed into the human body by the gastrointestinal tracts.

People at risk of arsenic exposure should be warned about the health hazards associated with arsenic. Tubewell water can be replaced by surface water. However, people should be educated to boil surface water before drinking to avoid the affliction of infectious diseases. Utilization of domestic arsenic removal devices are encouraged to obtain clean water. Adding alum or ferrous salts to arsenic-contaminated water to convert arsenic into insoluble substances is one of the methods. Rainwater harvesting can be helpful at a low cost during the monsoon season. Handy and low-cost technology

to detect arsenic components in water can be applied to identify safe water sources.

The successful eradication of blackfoot disease in Taiwan set an exemplar in the public health approach for the prevention of arsenic-related health hazards. Because of the link between the etiology of these endemic diseases with the artesian well water, the Provincial Government of Taiwan began to implement tap water supply systems to replace the artesian well water in the endemic areas. Programs that moved villagers to other residential areas had even been carried out in some seriously affected villages. Since the 1970s, the incidence rates of blackfoot disease decreased dramatically after the implementation of these public health measures. The eradication of blackfoot disease by changing the water supply system also demonstrated an excellent example that many environmental diseases can be successfully eradicated by removal of their vectors, even when the real etiology remains controversial.

See Also the Following Chapters. Chapter 6 (Uptake of Elements from a Biological Point of View) • Chapter 9 (Biological Responses of Elements) • Chapter 12 (Arsenic in Groundwater and the Environment) • Chapter 23 (Environmental Epidemiology) • Chapter 25 (Environmental Pathology) • Chapter 26 (Toxicology) • Chapter 27 (Speciation of Trace Elements)

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