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Chemicals and Society

Life on planet earth can be scientifically described at a number of different levels. A lake or a forest can be defined as an ecosystem which consists of many different species and many individuals of each species. Some organisms, for example, mammals, are composed of various organ systems, such as the respiratory system, which is made up of organs composed of tissues and cells. A cell is normally considered to be the smallest unit of life, but cells in turn contain various components which take care of important cell functions such as the generation of energy and the construction of proteins. The composition of such cell organelles may appear complex, but today we know in principle how they are made up of biomolecules such as amphipathic compounds, proteins, and nucleic acids. The various processes that take place in a cell can in most cases be described in detail on a molecular level, and chemical structures and chemical reactions are ultimately responsible for all cellular functions. It has been calculated that the number of chemical reactions that keep a relatively simple unicellular organism like a bacterium alive is approximately a few thousand. The cell of a mammal is of course much larger and more complex, and is still not understood in all details, but it is reasonable to assume that our cells owe their status as living things to a certain number (more than a few thousands but still finite) of chemical reactions. Such chemical reactions comprising life can be affected by many things, and this book will look more closely at how various chemicals can disturb them and what consequences that may lead to.

The first chapter will simply introduce the reader to the background, some general aspects of hazardous chemicals, and how society responds to them. The key conclusion of Chapter 1 is that the lack of knowledge concerning hazardous chemicals is alarming, but that fundamental understanding of the relationships between chemical hazards and chemical structure/properties will help anyone handling chemicals to protect himself or herself as well as the environment.

1.1
Basic Problems

There are a number of important basic problems that must be considered when the effects of chemicals on health and the environment are discussed. Some are

Chemistry, Health, and Environment. Olov Sterner

ISBN: 978-3-527-32582-5

BEWARE OF DIHYDRO MONOXIDE (DHMO)

Recent reports have drawn attention to a chemical that should be handled with the outmost care. The name of the chemical is dihydromonoxide, abbreviated DHMO, a deceptively tasteless and odorless chemical that yearly kills thousands of men, women, and especially children. DHMO is used in enormous quantities by the chemical industry, for instance, in nuclear power plants, and its use as an additive during the preparation of so. called junk food has been demonstrated. The presence of high concentrations of DHMO in tumors has recently been reported. In addition, DHMO is a main component of acid rain, and the large amounts of DHMO in our atmosphere make a significant contribution to the greenhouse effect. Military sources have revealed that thousands of tonnes of DHMO are distributed through special underground tube systems to, among others, secret weapon research plants.

Figure 1.1 A newspaper article that so far has not appeared.

self-evident, for example, the fact that the number of people on earth is increasing rapidly and that more and more chemicals are used for various purposes. Others are more difficult to define. Consider, for example, the fictitious newspaper article shown in Figure 1.1.

At first glance one may be concerned by this information, but a chemist would rapidly realize that the chemical DHMO is nothing but ordinary water. However, there are no lies in the article; everything said is in principle true. Thousands of people are killed by water yearly in drowning accidents, it is certainly used in large amounts by nuclear power plants, it is an ingredient in most ‘junk foods’, and it is a major constituent in tumor cells just as in any other cell. Rain is water and acid rain is mostly water, gaseous water in the atmosphere will reflect heat radiation from the earth just as the more famous greenhouse gas carbon dioxide, and tap water is distributed to most industries, including secret weapon research plants (this fact could have been revealed by any source, including a military source).

However, whereas a chemist reading this article will quickly see the joke and understand what the name DHMO stands for and what properties this chemical has, a person with no background in chemistry may be caused severe anxiety. If instead of water we choose a less well-known chemical that even chemists are unfamiliar with we may imagine a situation where a chemical is described in different and completely contradictory ways, for example, as a relatively nonhazardous chemical that can be handled safely (by a manufacturer or a person that has worked with the chemical for a long period) or as a dangerous and hazardous chemical with which all contact should be avoided (by someone suffering from chemophobia). Few are able to assess information about chemicals critically and react to it in a completely rational way.

The example in Figure 1.1 illustrates several points:

1) that the hazards of a chemical can be described, formally correctly, in several different ways,
2) that chemical hazards cannot be defined in absolute terms, and
3) that different hazards cannot be compared.

People perceive hazards in very different ways. Some have chosen to be smokers and/or to consume alcoholic beverages in spite of the fact that they are well aware that such habits will expose them to chemicals that in the long run will increase the risk of acquiring lung cancer and/or damaging the liver. The reason may be that they underestimate the risk, or they think the benefits of smoking and drinking outweigh the risk of damage. While such decisions perhaps can be left to the individual, others are more complicated and difficult, affect many people, and should consequently be based on very solid knowledge. For example: Should we produce electricity by nuclear power plants or by burning fossil fuels? We know that accidents in nuclear power plants will leak radioactivity to the environment, and that is certainly a severe hazard, but on the other hand we strongly suspect that the carbon dioxide added to the atmosphere by burning fossil fuels will increase global warming. Which hazard is more dangerous? Ask two people and you are likely to get two answers. There is simply not a straight yes or no answer to a question like: Is chemical X dangerous?

We will get back to this question several times in this book, simply because it is so fundamental. Not only do different people perceive hazards differently, but commercial enterprises (manufacturing and selling chemicals) and government authorities (regulating their use and depending on the taxes they generate) will have their views on chemical hazards that are not necessarily the same as yours or mine. One should also be aware that in some situations there may be pressures, for example economical or political, to twist the truth about chemical hazards in order to gain some kind of advantage.

By definition, a chemical hazard is the result of the intrinsic properties of a chemical or a situation involving chemicals that in particular circumstances could harm humans and/or the environment and/or damage property. Highly toxic compounds may be considerably less hazardous than a relatively nontoxic chemical, depending on the conditions under which they are used. A risk differs slightly from a hazard in that it also considers the probability that a hazardous chemical will cause the harm or damage that is has the potential to do. However, the two terms are often used as alternatives.

1.2 Definition of the Sciences Involved

The issues that will be discussed in this book are interdisciplinary, although they will mainly be described from a chemical viewpoint, and we may note that the following major scientific disciplines are involved:

Organic chemistry describes the properties and reactions of organic compounds, which in principle are all compounds that contain carbon, while *inorganic chemistry* deals with chemicals that do not contain carbon (exceptions are, for example, metal carbonates, carbon dioxide, and carbon monoxide, which are considered to be inorganic). As well as carbon, organic compounds can contain virtually any other element, but the vast majority of them are only composed of carbon, hydrogen, oxygen, and nitrogen. Almost all the chemicals that take part in the chemical processes that keep organisms alive are organic, and the study of such processes is carried out within the discipline *biochemistry*. Most compounds that are known to have toxic effects are organic (most of the toxic inorganic compounds considered in this book contain toxic metals), and it is obvious that the carbon atoms of organic compounds play a central role from the point of view of their structure and properties. As an atom with four valence electrons, the carbon atom has a strong tendency to make chemical bonds to four other atoms in order to achieve the stable electronic configuration of the noble gases. Carbon readily makes chemical bonds to a range of other atoms, including carbon itself, and compounds containing only a few carbon atoms can form a large number of different molecules. Figure 1.2 indicates how the structures of organic compounds composed of a certain number of atoms can be varied almost infinitely, simply by changing the positions of the bonds between the atoms. Even without considering the stereochemistry of the substituents on the rings and the double bonds, there are 44 compounds in Figure 1.2 all having the elemental composition $C_5H_{10}O$ and all having different chemical properties.

The carbon atoms will normally provide the backbone of an organic molecule, while the heteroatoms will constitute functional groups that give the compound its characteristic properties (discussed in Chapters 2 and 3). Adding to the usefulness of organic compounds, the energy of carbon–carbon and carbon–hydrogen bonds is high, which makes organic compounds suitable as energy sources for, for example, the biochemical reactions (discussed in Chapters 3, 4, and 7).

Although we will not get involved in any intricate biological problems, we will discuss some aspects of *toxicology* and *ecotoxicology*. Toxicology in general deals with the study of poisons and their effects on single organisms, especially on humans, while ecotoxicology is concerned with the effects on ecosystems. The difference should be noted; while an effect of one chemical on one or more organisms may be dramatic (e.g., death) the effect on the ecosystem could well be negligible, and vice versa. The term *environmental toxicology* usually indicates that the interest is focused on what effects chemicals have on the environment and how these effects affect humans, for example, the contamination by pesticides of species used by humans as food. Environmental toxicologists are not primarily

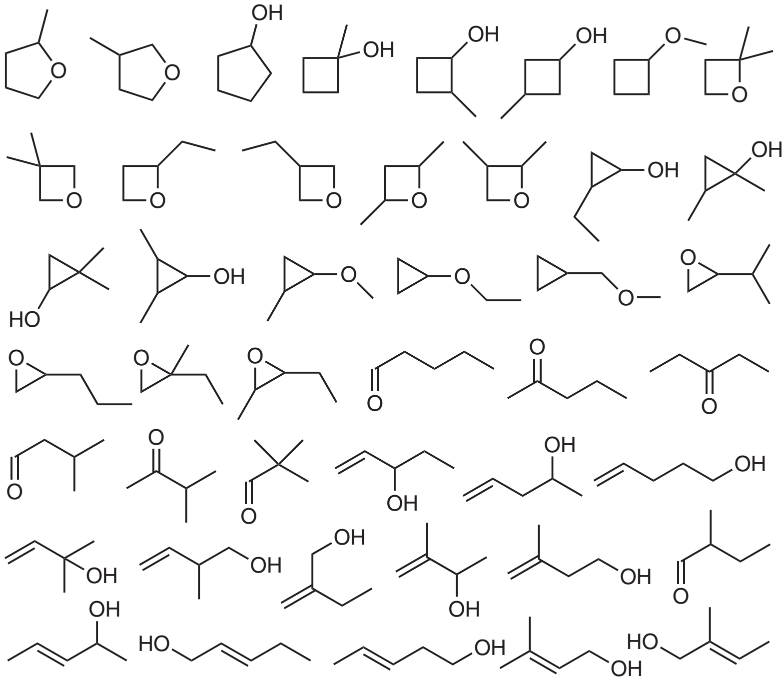

Figure 1.2 Examples of organic compounds having the composition $C_5H_{10}O$.

interested in the effects on ecosystems. The main focus in this text will be on the chemical properties that are associated with toxic effects (directly or indirectly) on humans, for which the term *chemical toxicology* may be the most appropriate.

1.3 Trends and Developments over the Years

Anyone who has been working for a long time where chemicals are handled will have noticed that chemicals are treated differently today compared with, say, 10 or 20 years ago. Attitudes have changed, procedures have been improved, and regulations are more strict. Some decades ago, chemicals were handled in ways that could lead to health problems, but this is no longer considered acceptable. While chemical waste in those days was simply buried or discarded into the nearest river, it is today taken care of and destroyed by means of specially developed processes. Also, new bioactive chemicals were invented that, for example, could be used to treat illnesses and control pests, and that initially were considered to be miraculously suitable for their task but later turned out to be hazardous. Examples are the insecticide DDT (DichloroDiphenylTrichloroethane) and the biocide 2,4-dinitrophenol, which was later used in slimming cures (see Figure 1.3).

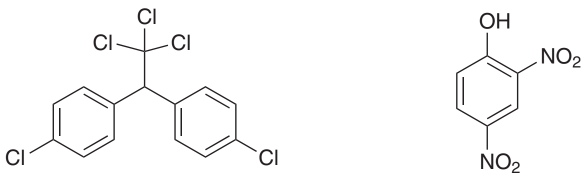

Figure 1.3 The structures of DDT and 2,4-dinitrophenol.

DDT, an old compound that was rediscovered in the 1930s when it was found to be a very efficient insecticide, was used extensively during World War II and the following decade. It was, in those days, important for the successful control of illnesses (typhus and malaria in particular) that are spread by insects, and saved the lives of a great number of people. The effects of DDT were truly remarkable, as the incidence of malaria in a small country like Sri Lanka shows. Here, 2 800 000 cases of malaria were reported in 1946, before the days of DDT, but only 110 cases in 1961 after DDT had been used for several years, and then again 2 500 000 in 1969 after DDT had been banned for 4 years. However, something that was not considered was that DDT is an extremely lipophilic and stable compound which is not degraded in our environment but is instead efficiently extracted by organisms. Some species (e.g., birds of prey) at the top of the food chain eventually accumulated so much DDT that their reproduction was threatened, and had the use of DDT continued on the same scale other species including man would have been in danger. The 'magic bullet' against insects became an environmental nightmare, and we shall return to DDT and similar compounds later in the book.

2,4-Dinitrophenol, an old pesticide, was launched in the 1930s as an efficient slimming agent for people who wanted to lose weight. It is indeed efficient, blocking the production of energy which is normally associated with the degradation of nutrients and stimulating the body to consume more nutrient (e.g., fat) than it needs. The only problem was that a slight overdosing could be fatal, and many accidents took place. It was therefore eventually banned as a slimming agent, and in the 1970s it was even considered to be too toxic even for use as a pesticide and banned for this purpose in many countries.

Thus, knowledge about the hazards associated with the use of chemicals has increased over the years, often in what we may call 'the hard way' – by making mistakes and learning from them. This has led to extensive regulation of the use of chemicals, and is the subject of the next section. The purpose of such regulations can be said to be to protect man and the environment from the hazards of chemicals. Today we may regard the misjudgments made in the 20th century as somewhat foolish and due to lack of knowledge, but it would be very stupid indeed to consider the level of knowledge we have today to be complete. Nor should we count on legislation to protect us from chemical hazards completely, even if everyone followed the rules. Instead, we may be sure that 20–30 years from now experts will look back and comment on the senseless use of chemicals X and Y and how this led to serious problems that could easily have been avoided 'if only they had known what we know now'. And they in turn will be the victims of the same hindsight after a further 20–30 years ...

The conclusion, which is valid most of the time, is: Things have improved, but they are not perfect.

1.4 Legislation

The legislation that regulates the use of chemicals aims to avoid all avoidable risks to both man and environment associated with chemicals, just as traffic rules are intended to protect people from traffic accidents. However, as we are all strongly aware, society as we know it will not function without chemicals or without traffic, and even if the intentions of the legislators are the best it is simply not possible to reduce the risks to zero, whether they are due to traffic or chemicals. So, at the same time as the legislation protects against chemical hazards it must also provide the means to use economically important chemicals, some of which are known to be carcinogenic, for example, but in spite of their toxicity are allowed to be used in workplaces. Nevertheless, modern legislation has improved the working conditions in industry immensely, and has also managed to decrease the pollution of the environment considerably. Any activity involving the handling of chemicals, for example, a business, will be regulated by a number of laws, rules, and regulations, and anyone who intends to take part in such an activity must get acquainted with quite a lot of legislative text. Thus, knowledge of the law is almost as important as knowledge of the hazards, and ideally would be a major topic in a text like this, but for two reasons this cannot be the case. Firstly, the legislation differs from country to country, even if the chemical hazards and the people that should be protected are identical, and it is not possible to discuss 'average' laws. Secondly, in contrast to the chemical hazards that the legislation should protect us against, the laws change frequently following new discoveries, improved or deteriorating financial situations and so forth, and any discussions of laws and regulations therefore become out of date quite quickly.

The legislation may regulate in detail which chemicals are permitted, making sure that only chemicals that have been proven to be sufficiently safe are approved. However, that kind of legislation is unusual and normally only applies to certain compound classes (e.g., pharmaceuticals, pesticides, and food additives). In most countries it regulates the concentrations of the most frequently used chemicals that are allowed in the respiration air in workplaces and how chemical waste from different kinds of activities should be treated. In most countries there are also rules that ensure that the labels on containers for chemicals has information about any associated hazard, that more comprehensive information is available to those who purchase and use a chemical, and that workplaces where chemicals are handled are equipped with safety devices such as gas masks and fire extinguishers. The competence (education and training) of persons handling chemicals is not regulated in any detail, but this is of course a critical point, as anyone with a good

<u>CAUTION</u>
Chemical X may be harmful if inhaled. Chemical X may cause irritation. Chemical X may cause a rapidly-developing pulmonary insufficiency, labored breathing, and cyanosis followed by cor pulmonale and short survival time. Death may result from cardiac failure or destruction of lung tissue with resulting anoxia. Skin contact may cause irritation and dermatitis. Eye contact may cause redness, irritation, and conjunctivis.

<u>TARGET ORGANS AFFECTED</u>
Eyes, skin, and mucous membranes.

<u>FIRST AID — INHALATION</u>
Remove from exposure area to fresh air immediately. Keep person warm and at rest. Get medical attention immediately.

<u>FIRST AID — SKIN</u>
Remove contaminated clothing and shoes immediately. Wash with soap and large amounts of water. Get medical attention.

<u>FIRST AID — EYES</u>
Wash eyes immediately with large amounts of water for 15–20 minutes. Get medical attention.

Figure 1.4 Information about health hazards on the container of chemical X (*cor pulmonale* is a heart disease resulting from disease of the lungs or pulmonary circulation).

understanding and knowledge about a hazard will be able react adequately. It may be argued that competence is even better than regulations in some instances, although a combination of the two may well prove best in the long run. The example shown in Figure 1.4 illustrates this.

Unlike the example in Figure 1.1, this has been taken from real life and is not made up. Anyone with a bottle of chemical X in his or her hand will be concerned on reading the warnings: X is obviously a chemical to treat with caution and respect. However, chemical X is in fact sea sand, a product that is used in the chemical laboratory for various purposes but is not associated with any dramatic hazards. Indeed, many of us dream about spending time on a sunny beach consisting of sea sand, and the idea that this should pose a hazard is for most people far fetched. It is true that inhaling sea sand would give problems with respiration and that sand in the eyes is painful, but this really comes as no surprise. This is in fact an example of a reaction of the producer, the chemical company, to a situation where they may be accused of not warning the consumer of any imaginable hazard, never mind how unlikely it is. For many, the initial feeling of respect for chemical X will be replaced by confusion, quickly followed by a feeling that information about health hazards exaggerates the risks. In such a case, the law is of little value, and users of chemical X may instead choose to rely on their own judgment, based on knowledge about chemical hazards and experience of handling chemicals.

1.5
Knowledge about Chemical Hazards

Knowledge about the effects of chemicals on man and the environment is crucial, as is the good sense to use that knowledge in a sensible way. Knowledge can be acquired in many ways, but if the effects of a chemical are described in the literature this is the first place to search. Today, huge databases where information about chemicals can be sought are available not only in chemical libraries but also via the internet. However, surprisingly few of the approximately 50 000 – 100 000 chemicals used today have been studied from a toxicological and ecotoxicological viewpoint, and for only a few percent of these can we can say that we have complete knowledge (which includes long-term toxicity, e.g., carcinogenicity) about their effects on man. In general, the chemicals that have been the most thoroughly studied are those that the legislation requires to be tested before they are approved. A pharmaceutical compound, for example, must be shown to be relatively safe before it may be used. Bulk chemicals, on the other hand, although they are used in large quantities in the chemical industry, are not subject to such regulations, and little is known about the toxicity of most of them. In addition, they may contain considerable amounts of impurities (several %) which are not even declared on the label of contents. Many bulk chemicals have been used for decades, and over the years we have had some experiences with them that indicate to us in what situations they may be hazardous, but even if a chemical appears from experience to be safe this is no proof that it really is so. Taking carcinogenic chemicals as an example, all chemicals that have been proven to be carcinogenic to man have been studied in epidemiological investigations where the exposure to a chemical (at a workplace for example) is correlated with the incidence of cancer 20–30 years later, and this is compared to a nonexposed control group. However, it is quite difficult to demonstrate such correlations (it has only been done with 30–40 chemicals), because it requires either (a) that the chemical is a potent carcinogen (e.g., bis-chloromethyl ether, formerly used for the manufacture of ion exchange polymers), (b) that the group exposed is huge (e.g., cigarette smokers vs nonsmokers) or (c) that the tumor formed is extremely unusual (e.g., vinyl chloride, which is a weak carcinogen, causes a very unusual form of liver cancer). Carcinogenic chemicals that are not potent, are not used by very large or isolated groups, and do not cause unusual cancers will not be detected by epidemiological investigations because their effects will not be noticeable from the number of tumors formed spontaneously.

An interesting example of a chemical that has been used for a long time (more than 100 years) and that we have a lot of experience of is acetylsalicylic acid (see Figure 1.5). This is used as an anti-inflammatory agent, as an antipyretic, and as an analgesic, and recently its ability to inhibit the ability of the blood to coagulate has been taken advantage of for the treatment of thrombosis. Acetylsalicylic acid is a derivative of salicylic acid, as is salicin, the active constituent of the bark of the willow tree (*Salix alba*). In the latter part of the 18th century, Reverend Edward

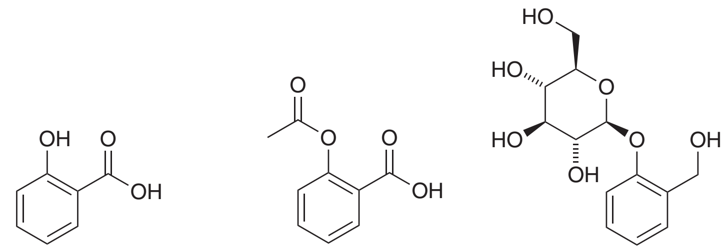

Figure 1.5 The structures of salicylic acid and two of its derivatives.

Stone, inspired by a local woman's tale and by the bitterness of the bark, believed that it would have the same effects as Peruvian bark (containing quinine) and treated a number of people suffering from fevers with the bark. The treatment was successful, and the salicylic acid derivatives obtained from willow bark as well as from the plants meadowsweet and wintergreen became important agents to reduce fever and pain and to relieve gout and arthritis. The acetylated derivative was prepared in the end of the 19th century by the German company Bayer AG and sold under the name Aspirin.

It is not a nontoxic compound (10–15 g may damage the kidneys of an adult), but the long-term effects (e.g., carcinogenicity and teratogenicity) of low doses of acetylsalicylic acid are based on our long experience with human exposure and known to be negligible. However, in animal experiments it has been noted that acetylsalicylic acid has a weak teratogenic effect, and it is doubtful whether it would be approved if it was invented today.

The fact that we use so many chemicals without really knowing much about their effects on man and environment may come as a shock. The reason is of course economic; new knowledge is unfortunately not free, and the costs of assaying the toxicity and ecotoxicity of one chemical can climb to 1 million €. Even though the ambition today is to raise standards and demand more knowledge about all new chemicals that are added to the market, there are no possibilities to thoroughly investigate the toxicity of all the old chemicals already in use. It may seem logical to ban all chemicals until we know about their effects and can regulate their use, but such an action would overturn society. Instead, we will have to learn to live with this situation for many years to come. If knowledge about the hazards of a chemical cannot be found in the literature, and if it is considered to be too expensive to carry out the necessary biological tests by oneself, the only alternative is to make intelligent guesses based on known relationships between chemical structure/chemical properties and toxicity/ecotoxicity for similar compounds. This is essentially what this text aims to do, to show the reader that the effects on man and environment that we want to avoid are caused by chemical properties that we to a large extent can understand by analyzing the chemical structure. In the future it is believed that such intelligent guesses, made by computers that have been fed all available data and taught to analyze the data in a relevant way, will be used routinely to sort out old chemicals that we know too little about but which have chemical properties that the computer has associated with toxicity, as well as chemicals in the pipelines of development but classified as potentially hazardous. However, until the day when computers take over the decision-making, it is good advice try to maintain the ability to make judgments for oneself.

1.6 Acceptable Chemical Risks

At the bottom line we will find that all chemicals have some hazards associated with them, although the differences between those regarded as 'safe' and 'hazardous' are enormous. Toxicity and ecotoxicity do not come in black and white but as a gray scale, and apart from deciding if and how a chemical is hazardous we need to know something about its potency. This can be done by relating the toxic response of a chemical to the dose, and an example is shown in Figure 1.6, where the carcinogenicity of two chemicals is plotted against the dose. There is an obvious relationship between dose and response, which can be approximated with a straight line (obtained by statistical analysis of the data or simply by putting a ruler along the crosses and circles). The slope of that line would be a measure of the potency of the compound. The slope of the line corresponding to the crosses is greater than that corresponding to the circles, and it is thus possible to compare the carcinogenicity of the two chemicals.

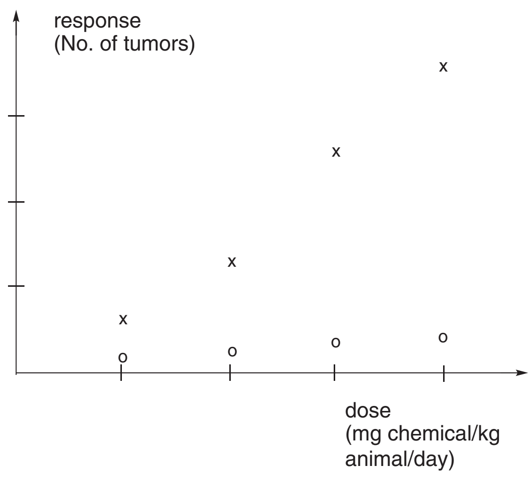

Figure 1.6 Dose-response relationships for two carcinogenic chemicals.

Before we start to use them, let us define some common terms:

in vitro This means 'in the glass' and indicates experiments carried out with cells or tissues in test tubes or equivalents.

in vivo This means 'in life' and indicates experiments carried out with living organisms.

The next difficulty is to translate our knowledge about the toxicity of a chemical, which in almost all cases refers to *in vitro* assays and animal experiments, to the species that we are interested in, namely *Homo sapiens*. It is also not obvious whether it is relevant to use data from animal experiments where the doses used are much higher than those to which humans would be exposed. These problems will be discussed in more detail in Chapter 7, but in general the knowledge that we have acquired is not enough to make an absolutely certain assessment of the toxicity to man, and approximations have to be made. Finally, knowing about the ifs, the hows and the how muches, we have to decide which risks are acceptable in different activities. Obviously we have to accept all kinds of chemical hazards, even genotoxicity, but we can still regulate, for example, what concentrations of a carcinogenic chemical we consider acceptable in the respiration air at a place of work. Some chemicals, for example, pesticides and preservatives, are considered by many to be unacceptable as they in general are toxic to at least some organisms, but they also save human lives by improving crops, killing disease carriers (e.g., DDT, *vide supra*), and avoiding food poisoning by bacteria. Decisions on what risks we are ready to accept in order to benefit from the various uses of chemicals are extremely difficult, as we have already noted, as individuals as well as authorities and companies value risks and benefits associated with chemicals very differently. In addition to the scientific and humanistic dimensions, there is also a political aspect, as the safety of people and the protection of the environment have to be considered together with economic factors. Looking back, there are examples of chemicals that have received exaggerated attention (because of lack of knowledge, suspicion, fear, and/or political opportunism) while others have not received the attention they merit. One of the major threats today is that the rapidly increasing concentrations of carbon dioxide and methane in the atmosphere, formed by combustion of mineral fuels and by anaerobic fermentation, will affect the climate and thereby the weather systems of the earth. Little is today known about this so-called greenhouse effect (it will be further discussed in Chapter 10), but if it exists and the additional carbon dioxide and methane do change the climate in a dramatic way, we will be very sorry that we did not take action sooner.