Chapter 5

From Prevention to Precaution—Valuing Risks

The Nettles farm is home to some 100 dairy cows. The farmer and his family live a hard but fulfilling life, providing prime cheeses to the local market. Until one day the competent authorities pay the Nettles a visit on the suspicion of the use of illegal antibiotics. They take some urine samples and find parts per billion of some breakdown products (metabolites) of the drug furazolidone, which is not allowed in animal rearing. The reason for this ban is the suspicion of carcinogenic qualities of the primary drug and its metabolites. Therefore, in the European Union, a zero-tolerance policy is in place for chemicals such as this antibiotic. That simply means that the antibiotic and its metabolites should not be found in the cow's meat, organs, urine, and manure on any concentration level whatsoever, or as low as can be analyzed. As a result, the Nettles lost their cows—they were killed by order of government officials in order to protect public health—and almost their farm.

CHEMICALS—ASSESSING RISKS

The dose makes the poison. Probably the oldest and most famous discovery and axiom in toxicology stands at the heart of any analysis of risk when in contact with chemicals. Again, any chemical can be a risk to our health, even water. Thus, risk of chemicals in our environment—air, water, soil, food—is all about concentration levels of exposure. How do these different levels of exposure compare? How much for instance is a part per million (ppm), or billion (ppb), or trillion (ppt), the much-used terms in describing concentrations of all sorts of (un)wanted chemicals in our environment.

Let's start with a ppm (10^{-6}). In terms of the International System of Units, i.e., 1 mg in 1 kg or 1 μL in 1 L. Some comparisons could clarify these numbers: 1 ppm is 1 minute in 2 years; 1 cent of €10,000; 1 teaspoon of DDT spread over 2 hectares of land (20,000 m^2); 1 drop (0.05 mL) of vermouth in 50 L of gin, rather a dry martini cocktail.

What about a part per billion (10^{-9}), i.e., 1 μg in 1 kg? It is 1 minute in 2000 years; 1 person in the entire population of India; 1 medium-sized crouton in a 500-ton salad.

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A part per trillion (10^{-12}) is 1 ng per 1 kg. It is 1 second in some 33,000 years; 1 square floor tile with sides of some 0.3 m on a kitchen floor twice the size of the Netherlands; 1 drop (0.05 mL) of vermouth in 50,000,000 L of gin, which is a very dry martini cocktail indeed.

We could go even lower to parts per quadrillion (10^{-15}), which stands for 1 pg per 1 kg. A ppq stands for one postage stamp on a letter the size of the states of California and Oregon combined; one human hair out of all the hair on all the heads of all the people in the world; 1.6 km on a journey of 170 light years (which is 1.6083×10^{15} km).

Now, these numbers give some context to concentration levels on which quite a few chemicals are regulated. Perhaps another way of giving perspective is figuring out the actual number of molecules we are dealing with when we talk about these levels. First, let's figure out how many molecules there are in an average tumbler filled with water.

To do this, we require Avogadro's constant, or the mole. Just like a dozen is 12 things of whatever, a mole is simply Avogadro's number of things, in chemistry that is atoms or molecules. The size of Avogadro's constant is quite large to say the least: 6.022×10^{23}. With this constant we can convert the directly measurable mass of, say, water into the actual number of water particles (H_2O), which we can't measure directly.

Let's assume we have 180 mL of pure water in the glass tumbler (Figure 5.1). That is 180 g of water, which amounts to 6.022×10^{24} molecules. So, 180 g/180 mL of water represents 10 moles of water molecules. A huge number. And the word huge doesn't even do justice to this number.

FIGURE 5.1 Picture of a classic table glass.

In fact, the number of water molecules in our glass closely outnumbers the amount of stars in the visible universe, which is estimated to be between 10^{22} and 10^{24} stars. That shows how many small molecules in fact are.

Adding sucrose (the normal sugar) to the pure water in our tumbler up to, say, 1 ppb would amount to adding just 0.18 μg of sucrose. That is, 3.167×10^{14} molecules of sugar. Again, this is a staggering amount of molecules, although the 0.18 μg could never be weighed in on a scale found in the average household kitchen. Specialized scientific scales are needed to be able to weigh such small amounts. Also, this amount of sugar in water is below our taste threshold, which is some 6 g of sucrose per liter, or roughly 1 g in our glass of water.

So, the world we are dealing with every day *and* the molecular world seem far apart in terms of mass and numbers of molecules, respectively. Although we can see the small and shiny sugar crystals we add to tea or coffee in the morning, the fact that these crystals are made up of so many discrete sucrose molecules baggers belief. Nevertheless, the macro of everyday life and the molecular of chemistry and toxicology are different expressions of the same thing.

Nevertheless, we are perceptive creatures and we can sense exposures to chemicals that are not agreeable to our physique, up to certain level of course. What toxicologists want to assess is at what levels of exposure we are safe, both on the short and the long term, and at what levels we need to take measures in order to lower or avoid exposures. Here, the natural

FIGURE 5.2 Picture of the classical risk assessment procedure.

sciences cannot provide all the answers. Because: how safe is safe enough? (Refer to Fig. 5.2.)

Now, the normal procedure in the field of toxicology is first to identify the hazard or hazards related to the chemical of choice. The hazard of a chemical is usually defined as the "inherent capability" to produce damage to organisms. Hazard identification encompasses gathering and evaluating data on the types of health effects or diseases that may be produced by a chemical at some dose. Additionally, exposure conditions under which environmental damage, injury, or disease will be produced need to be evaluated.

As soon as hazards are identified, the risks involved need to be assessed. A chemical that is hazardous to human health does not constitute a risk *unless* humans are exposed to it at a certain level. So the fact that hazards are known does not imply that we are by definition at risk. It all boils down to levels of exposure.

So the next step involves the appraisal of exposure levels. Not an easy task to perform. It involves estimating emissions from production in factories and household uses, and pathways and speeds of movement of a substance, e.g., through the air or water. Knowledge on its chemical and/or biological transformation and degradation is needed as well in order to obtain concentrations or doses to which human populations or environmental compartments are exposed.

It is obvious that exposure assessments are shrouded in uncertainties. The biggest unknowns are related to (1) the total emissions during production of the chemical, (2) the way it is used in society in all sorts of different products, and (3) the enormous geobiological variability across the globe such as climate, hydrology, geology, and biology, that influences the transport and transformation of the chemical.

Once we have a rough estimate of exposure, the effects related to such an exposure are mapped: the dose−response assessment. It is estimated what the relationship is between the level of exposure to a chemical (the dose), and the prevalence and severity of an effect or effects (the response). For that, a huge amount of information is required from experimental research with plants, test animals, and, very rarely, human volunteers. Also, population research (epidemiology) is done to tease out those effects that might be related to exposure to the chemical in question.

All these steps—(1) hazard identification, (2) exposure assessment, (3) effects assessment, (4) risk assessment—bring us to predicted or estimated no effect levels—NELs—for humans by dividing no observed adverse effect levels—NOAELs—found in laboratory animals or test systems using cells from animals or humans with some assessment factor, which usually lie in the range of 10−10,000. Assessment factors are numbers reflecting the estimated degree of uncertainty when experimental data from model systems (e.g., animal testing) are extrapolated to humans. Laboratory tests cover only

a small part of the variety of responses that may occur in human populations. Extrapolation from experiments to humans involves numerous scientific uncertainties and assumptions. The higher the assessment factor, the lower the NEL, expressing a more cautious approach to the studied chemical. Lower NELs articulate the idea that more people are protected. The NELs are expressed in tolerable daily intakes—TDIs. The TDI is the daily intake of a chemical that, during the entire lifetime, appears to be without appreciable risk on the basis of all known facts at the time.

Overall, this brings us the risk characterization of the chemical. Now, taking this risk characterization process at face value, it seems that any exposure to any chemical should be as low as possible. In fact, avoiding all contact with chemicals seems the best option anyway. As we already pointed out, that is impossible and even dangerous. We are made of chemicals (there is much more to being human than that of course) and need food chemicals to stay alive and healthy. Chapter 4, Nature Knows Best—Chemicals From the Geobiological Sphere, dealt with that. Besides, all toxicological research would then immediately be superfluous.

To get to grips with chemical risk characterization, risk management comes into play, as other aspects than scientific analyses are required to balance the decision-making process. Overall the risk management process carries at least the following as shown in (Fig. 5.3).

In a nutshell, risk assessment asks "How risky is this chemical"?, whereas risk management asks "What shall we do about it"? This regulatory decision-making has become more developed and elaborate in the

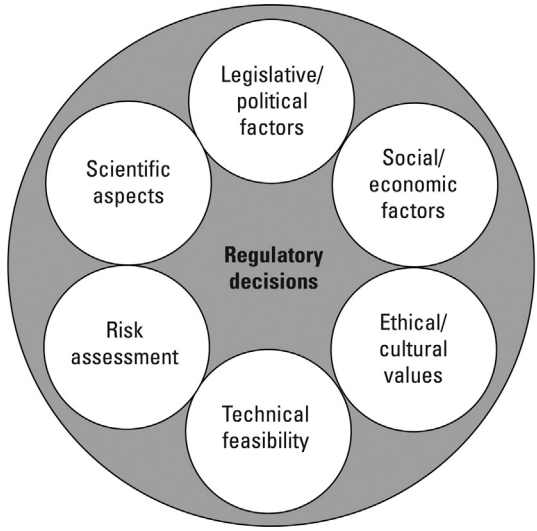

FIGURE 5.3 Risk management process (From U.S. Congress, Office of Technology Assessment, 1993. Researching Health Risks. U.S. Government Printing Office, Washington, DC.).

FIGURE 5.4 Products derived from crude oil.

20th century. In fact, since the industrial revolution we have expanded our visible chemical surroundings, and this process accelerated in the previous century. Production processes that use crude oil as the basis for many different products, for instance, add to the mix of chemicals that we are "exposed" to such as pharmaceuticals, coatings, polymers, computers, pesticides, printer cartridges, toys, cell phones, tools, plastic film wrap for food. The list is almost endless. These products bring us all sorts of benefits and are traded off against any potential risks they might engender in mining, production, and use (Fig. 5.4).

The process of risk characterization brings together scientific knowledge, however limited considering the complexity, and value judgments that when joined together produces some kind of regulatory outcome. Some outcomes could be a safety standard for use in industry and at home, a ban because it is deemed too risky to produce and handle, further research on the chemical, and so on. And these scientific knowledge and value judgments are expressions of the culture we live, which could well be called precautionary.

RISK CHARACTERIZATION IN A PRECAUTIONARY CULTURE

Precaution seems a harmless, even prudent word of common usage and is ostensibly synonymous with prevention. However, they should be distinguished so as to understand precautionary culture and the way we view chemicals. The chemophobia we discussed in the last chapter is very much embedded in this precautionary culture.

Prevention means avoiding damage rather than remedying it after the damaging event. The damage to be avoided is clearly defined as resulting from a specific process or product in a chain of events: cutting one's finger in a food processor; injury caused by a car crash; food poisoning as a result of consuming food-borne pathogens such as *Salmonella enteritidis*, being exposed to chemicals when one paints the indoor woodwork; and so on. Thus, prevention entails putting in place measures to ensure, up to a certain point, that an already identified hazard cannot materialize, or to reduce its likelihood. Painters for instance can wear paint-spray facemasks during their indoor work as to prevent exposure to paint solvents.

Precaution on the other hand means an action taken in advance to protect against *possible* danger, failure, or injury. Precaution, as is understood nowadays, essentially takes prevention a critical step further, by deciding not to postpone physical, legal, or political interventions to prevent potential damage. This is done on the grounds that although scientific evidence of a potential hazard is limited or even absent, the hazard can never be excluded even though it might never materialize. We even have a legal principle of precaution, which states that "where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation." It is also known as the triple-negative definition: *not* having scientific certainty is *not* a justification for *not* regulating, or just simply "when in doubt, don't."

In the risk characterization process described earlier, the move from hazard to risk is not really possible within the precautionary context. Scientific knowledge, no matter how elaborate, always carries limitations that make it impossible to characterize all the risks involved. Hazards of certain chemicals are then deemed enough to regulate on a precautionary basis.

Examples of precautionary regulation of certain chemicals are easy to give, especially for those chemicals that do not have an estimated NEL, and so no TDI can be estimated. That might be the case because toxicological knowledge is lacking, or if there are suspicions that the chemical involved could be carcinogenic, that will induce or promote cancer. We will discuss the latter more extensively in Chapter 6, Molecular Trepidations—The Linear Nonthreshold Model.

In Europe, zero-tolerance levels are in force for compounds without a TDI, meaning that banned chemicals should not be detected at all

especially in food products. Obviously, analytical chemistry is not equipped to detect "nothing," so always has a minimum technical level to detect a chemical. That is for most chemicals in the range of parts per billion to parts per trillion.

Now, the first thing to consider is that molecules travel around the world in such a way that concentration levels of all chemicals are spread as evenly as possible. We know this phenomenon intimately—entropy; the progression to thermodynamic equilibrium, the heart of the second law of thermodynamics—from simple things. When sugar is added to a hot cup of coffee, the sugar dissolves and spreads evenly throughout the coffee. What you will never observe is that the just dissolved sugar suddenly returns to a lump of undissolved sugar at the bottom of your morning brew. Entropy drives the inexorable diffusion (spread) of chemicals throughout this world. The fact that we are literally stardust (again, and much more than that) could not be a better description of this diffusion process operative in the cosmos!

Second, some chemicals that are regarded as worthy of regulation—a pesticide, an antibiotic, an antifouling agent on ship's hulls, and so on—are explicitly regarded as synthetic, man-made, so if you find these in the environment or food, then an installed ban is easily enforced and by default deemed as effective. When it is found it has been illegally used; once people stop using the chemical it will simply disappear because of dilution and degradation. So the Nettles family in the beginning of this chapter have to face the consequences of their illegal labor. The detection of some breakdown products (metabolites) of the banned drug furazolidone is enough indication for the competent authorities to conclude that they used an illegal drug in their cows. But is that true?

We already pointed out in the previous chapter that the so-called synthetic chemicals might very well have natural sources as well. This has been shown extensively for organohalogens, which were once regarded as exclusively man-made. So what about furazolidone and its marker metabolite 3-amino-2-oxazolidinone (AOZ)?

The trust competent authorities place in such marker molecules is misplaced, as history shows. In 2009 there was an increased incidence in Belgium in the detection of semicarbazide (SEM), a marker molecule for the banned antibiotic nitrofurazone, in the freshwater prawns *Macrobrachium rosenbergii*. Nitrofurazone belongs to same class of antibiotics as furazolidone.

This was in contrast with all other European countries where no significant increase in SEM positive samples was reported. A possible explanation for this phenomenon was that at request of the Belgian Federal Agency for the Safety of the Food Chain, all approved laboratories were asked to analyses complete prawns (meat and shell) for the presence of metabolites of nitrofurans from December 17, 2004, onward. This procedure is not common in other countries, as only the meat is sampled.

SEM as a marker for nitrofurazone was already questionable as it was found that certain food production and packaging circumstances resulted in the formation of SEM. Experimental research later showed that crustaceans produce SEM at varying concentrations. The source of SEM, now positively identified as a natural metabolite, is unknown as of yet.

Clearly, SEM cannot be used as a marker molecule for the illegal use of nitrofurazone. The purported legal link between the presence of SEM and the prohibited use of nitrofurazone is broken. The fact that SEM is a natural metabolite in crustaceans rules out the possibility to track illegal nitrofurazone use through the use of SEM as a marker.

The idea that an unambiguous causal link can be made between the detection of some banned chemical and illegality in food production is overall untenable. Chloramphenicol, another banned and purported man-made antibiotic, roused quite the food scare at the beginning of the 21st century. Here as well, presence was regarded straightforwardly as the result of illegal use. However, unsurprisingly, it has been found as a natural component in plant material, which is used as animal feed through which it is transferred to animal tissue. This example is quite similar to the issue of the natural background of polybrominated diphenyl ethers (PBDEs) we discussed in the previous chapter.

Mother Nature thus amply supplies us with chemicals that we rather not have in our environment and our food. We even try to organize this by law, which clearly she doesn't abide by. And although we haven't found a natural source yet for AOZ, the marker molecule for furazolidone, history and chemistry learns that we most likely will. The question then arises why we would have zero-tolerance laws in the first place? Is it about hazards and the exposures thereto, or eradicating illegal use of chemicals (which does happen), or perhaps something else? It seems clear that the hazards-discourse so favored by regulators and politicians is the goal of choice, and the eradication of illegal use piggybacks thereon.

PRECAUTION AND ETHICS

In order to gauge the depth of this, we have to go back to the risk characterization of chemicals. This seems a very straightforward process that neatly separates science from regulation. But things are never that simple as we already have seen. We live in an age where safety should be maximized and if chemicals are suspected of hazards of especially a carcinogenic kind, everything must be done to ensure their absence from the environment to which we are exposed. That is the precautionary response: "when in doubt, leave it out."

So, when reviewing the risk characterization process, assessment factors can be dialed up as to make the NELs as low as possible. There is even a term for that: ALARA—as low as reasonably achievable. But reasonableness

is known for its elasticity, that might be stretched to even the idea that some chemicals simply should not exist, expressed as zero tolerance.

As the assessment factors are an expression of the uncertainty surrounding the scientific process of uncovering the risks of exposure to chemicals, precautionary culture feeds off this uncertainty. Precautionary politics in principle is never satisfied with research showing that no adverse effects have been reported at a certain level of exposure, the basis for an NEL. As "absence of evidence" is not considered to be "evidence of absence," proponents of precaution stress that adverse effects in spite of all the available evidence may yet arise in the (far) future. Our safety, security, health, and longevity should be guaranteed by science.

In precautionary culture then, science finds itself between a rock and a hard place: a very high level of skepticism with regard to what science cannot and should not do—give a chemical a clean bill of health—goes hand in hand with a very high level of confidence regarding what science is supposed to deliver—give a chemical a clean bill of health. So, science is never free from the culture in which it has grown from a scientific discipline into an overarching advisory role for society and politics on what is safe and what is not in the "chemical world." And of course, very few things are really safe, as with precautionary culture we have stepped into a realm of perceived *absolute* safety.

So, if even science cannot guarantee our chemical safety, then regulation should do the rest. And that it has done, or so it seems. It should therefore not be surprising that we are bombarded with chemical scares through press releases, newspaper items, new and widely advertised more stringent laws, and so on. We have become a scared people, tying in nicely with the chemophobia we discussed previously.

That leaves us with the one question, namely how to value risks of chemicals exposures, including those chemicals we do not want and we have banned from our environment to which we are exposed to daily. A number of issues are encapsulated in this not so simple question.

For one, science knows quite a bit of many different chemicals, and we should take that knowledge seriously, but *not* as definitive. Things change and so does science. The more we know about the chemical and toxicological world, the more we are baffled by its complexity. That brings us to the second point.

We are adaptable people. That is what we do: we adapt. As said earlier, we are exposed to thousands and thousands of different chemicals every day and we adapt to those chemicals, including the carcinogenic stuff we naturally find in our environment. And the better we can adapt, the better our health is. In fact, we "train" ourselves through that massively diverse exposure: eating healthy is related to a diversified diet, and that means more chemicals, not less.

Third, those chemicals that are regulated simply caught our attention, especially if these chemicals are produced industrially. It also shows that we regulate the so-called simple stuff, the chemicals we can "see." We simply ignore the rest, and for good reason. There is simply too much to research and regulate. That the simple regulated stuff sometimes surprises us through Mother Nature should *not* be surprising. And then we lose interest. Dioxins were all the rage in the 1970s and 1980s as it was advertised as the most toxic man-made chemical ever. And then we discovered natural sources of this not so toxic compound after all, even in ourselves. Very few people discuss dioxins nowadays.

Fourth, precaution has made us very wary of anything chemical, paradoxically combined with a lack of general knowledge of the chemical. That drives many different research efforts and very public displays of force, such as the killing of all the cows on the Nettles farm, which in fact is an actual case that we have anonymized.

The last aspect is material for our next chapter. We so much fear carcinogenic chemicals that we evaluate them separately in comparison to all other chemicals that are not regarded as carcinogenic, at least as far as we know. We think that every single molecule of a carcinogenic chemical could cause cancer. Whether or not that is even remotely true we will delve into next. Nevertheless, that is how we regulate such chemicals into purported oblivion. And again and again, we find reality opposing that misplaced legalistic instinct.

REFERENCES AND FURTHER READING

Berendsen, B., Stolker, L., de Jong, J., Nielen, M., Tserendorj, E., Sodnomdarjaa, R., et al., 2010. Evidence of natural occurrence of the banned antibiotic chloramphenicol in herbs and grass. Anal. Bioanal. Chem. 397, 1955–1963.

Berendsen, B., Pikkemaat, M., Römkens, P., Wegh, R., van Sisseren, M., Stolker, L., et al., 2013. Occurrence of chloramphenicol in crops through natural production by bacteria in soil. J. Agric. Food Chem. 61, 4004–4010.

Hanekamp, J.C., 2015. *Utopia and Gospel: Unearthing the Good News in Precautionary Culture.* PhD Thesis. Tilburg University, ISBN 978-90-823225-0-7.

Hanekamp, J.C., Frapporti, G., Olieman, K., 2003. Chloramphenicol, food safety and precautionary thinking in Europe. Environ. Liabil. 6, 209–221.

Hanekamp, J.C., Kwakman, J., Olieman, K., 2011. Crossing the ecological threshold of scientific analysis, natural chemicals and global trade. Anal. Bioanal. Chem. 399, 2223–2224.

Hoenicke, K., Gatermann, R., Hartig, L., Mandix, M., Otte, S., 2004. Formation of semicarbazide (SEM) in food by hypochlorite treatment—is SEM a specific marker for nitrofurazone abuse? Food. Addit. Contam. 21, 526–537.

Purves, D., Augustine, G.J., Fitzpatrick, D., Hall, W.C., LaMantia, A.-S., McNamara, J.O., et al., 2004. Neuroscience, Third ed. Sinauer Associates, Inc, MA.

Saari, L., Peltonen, K., 2004. Novel source of semicarbazide: levels of semicarbazide in cooked crayfish samples determined by LC/MS/MS. Food Addit. Contam. 21, 825–832.

See <http://www.accessdata.fda.gov/CMS_IA/importalert_1153.html> (accessed 23.06.16).

See <http://www.wateronthewb.org/resources/conversiontables.html> (accessed 23.06.16).

See <www.unep.org/Documents.multilingual/Default.asp?DocumentID = 78&ArticleID = 1163&l = en> (accessed 23.06.16).

U.S. Congress, Office of Technology Assessment, 1993. Researching Health Risks. U.S. Government Printing Office, Washington, DC.

Van Leeuwen, C.J., Vermeire, T.G., 2007. Risk Assessment of Chemicals, An Introduction, Second ed. Springer, The Netherlands.

Van Poucke, C., Detaverniert, C., Wille, M., Kwakman, J., Sorgeloos, P., Van Peteghem, C., 2011. Investigation into the possible natural occurrence of semicarbazide in *Macrobrachium rosenbergii* Prawns. J. Agric. Food Chem. 59, 2107–2112.