Chapter 9

Toxicology in Science and Society—Future Challenges

By now it should be clear what a toxic compound is. Or are you now confused, but on a higher level? If so, that is a good sign. Because every compound can display toxic properties, but it is the dose related to our physiology that makes the toxin. This entails that even our daily food can be toxic to us, yet we have achieved the ability to adapt. This is the major thread that runs through our book you have now almost finished. What remains is a short overview what we have achieved and to take a look at the challenges that lay ahead.

TOXICOLOGY: FUTURE CHALLENGES IN SCIENCE

The human body possesses an elaborate coping ability. The rich capacity to handle chemicals compounds even explains the evolutionary success of aerobic life forms. These coping mechanisms make it difficult if not impossible to describe toxic responses in absolute numbers. The estimation of toxicity is always expressed as a chance, a chance of harm. In society these chances are frequently and regrettably erroneously defined as absolute damages. The increasing complexity of our society requires that we understand the meaning of the word chance. Journalists play a crucial role in this.

Also in the science of toxicology, the meaning of a toxic response in a homeostatic physiology might be more clearly demarcated as a toxicological tipping point. Changes can occur in a resilient system until this point of no return is reached. It forms a challenge for toxicology to understand and define these tipping points. The so-called threshold of toxicological concern (TTC) might be an interesting value in this respect. The TTC indicates that the body can cope with compounds until a certain threshold dose is reached where concern arises. This TTC alludes to this tipping point and toxicology becomes more in line with the notion of chance of harm and will probably be better comprehensible for nontoxicologists.

There are signs that toxicology already develops along these lines. The so-called big-data approaches are used to map the complete physiology and to subsequently describe the influence of exogenous compounds on this physiology chart. Critics doubt whether the complexity and indeed the

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flexibility of the human physiology render this a successful approach. On the other hand, optimists even state that this methodology will allow prediction of toxicological tipping points for a single individual: your own big data.

And here's the difference between big data derived from many individuals and one person. Probability does not imply cause; it could never do so. But if we could extract big data related to one person, we are not looking primarily at "averages" from many individuals (probabilities) but at mechanisms of physiology of one individual. Then, cause and effect come into view. And that is what is required to understand and tackle the tipping points from homeostasis to toxicity.

Experiments with one person ($n = 1$) would then be possible. As long as recovery of the dynamic biological system occurs fast, the resilience is abundant. When repair becomes slower a toxicological tipping point is near. Surely it forms a very attractive perspective to be able to predict with early warning systems at which stage perturbation of a biological system is such that a cellular system is no longer able to recover (Table 9.1). Indicators of resilience will undoubtedly be used to characterize our personal health status, the ability to adapt.

Unlike a drug with an expected and desired biological effect, a toxic compound can exert its effect via all kinds of perturbations. This makes it difficult to predict the toxic response of a compound.

The attentive reader noticed that we frequently used words like xenobiotic or compound or substance and not chemical as so many do. After all, all compounds can elicit a toxic response, not just man-made chemicals.

Toxicological knowledge is however focused on these man-made chemicals. They are easy to investigate because they can be purchased in pure form and in large quantities. The effects of the combination of compounds (food) remain a future challenge. Our understanding on combinatorial toxicity is scarce. This should not lead to unfounded fear and putative syndromes like "multiple chemical sensitivity" should not be advocated.

Public awareness prevails that combination of compounds offers frequently more danger than single compounds. However, just by realizing that food consumption is an ultimate form of exposure to a combination of compounds

TABLE 9.1 Why Are Xenobiotics Toxic?
Xenobiotics cause toxicity by disrupting normal cell functions "to a point of no return": – Via binding to and damage of proteins (structural proteins like enzymes) – Via binding to and damage of DNA (mutations) – Via binding to and damage of lipids – Via reaction in the cell with oxygen to form "free radicals" which damage proteins, DNA, and lipids

should be reassuring in itself. In fact, the diversification of food intake is beneficial to health, which thus points at the opposite: combinations of compounds frequently offer less danger than single compounds.

Prediction of toxic effects of compounds matures. However, in the foreseeable future, it will not be possible to sufficiently understand how chemicals are metabolized in the body from predictive computer programs and tests in cells alone. Although the improvement in analytical techniques will offer possibilities to work with minute doses in humans directly, thus skipping testing in animals.

Large epidemiological studies which frequently give rise to a lot of unrest should be conducted with more methodological rigor, similarly as in medical studies, with protocol, end points, etc. defined on forehand. The outcomes should be reported reluctantly without overstatements, keeping in mind that the smaller the effects, the less like the findings will prove to be true in the long run.

Also, we should move away from the rendition of standards in mass (milligrams, micrograms, nanograms). Rather, if anything specified needs to said on standards, the mole (Avogadro's number) should be the standard. The number of molecules gives insight into the homeostatic responses and capabilities of our physiology. Mass does not convey such information.

In 2012 Daniel Kahneman wrote the book *Thinking Fast and Slow*. Our brain works in two modes, the associative and rational mode. In toxicology, as in any other area of science, both are needed, the knowledge phase and the contemplative phase. Realization of our way of thinking can guard against toxicological judgmental glitches that can bring societal trouble.

TOXICOLOGY: FUTURE CHALLENGES IN SOCIETY

We have shown that there are two routes toward regulation: from toxicology to regulation and from legislature and regulation to toxicology. In both, toxicology plays a major role but with different functionalities. In the first one, science discovers and triggers a regulatory response to tackle the problem that arose from that discovery. In the second one, toxicology is subsidiary to the wishes and demands of the legislature. Here, the scientific work is more diffuse, as it is not always clear that toxicology is equipped to handle the legislature's demands.

The crux between both strands is academic freedom. The first drives toward discovery—the hidden structure of toxicological reality—whereas the second is driven by construction of topics that might or might not be an issue within the realm of research. As a result, the second route is far more prone to public and political drivers that have less to do with the epistemic drivers of science. Although the second route has less academic clout, the societal spin-off with respect to public reassurance has value in itself. Unrest about certain toxicological issues can have its detrimental public health effects. Toxicology is then the science of reassurance.

Risk communication is of huge societal significance to value the magnitude of the risk. Education remains of utmost importance. Some basic knowledge on how compounds interact with and on the human body and how compounds behave in the environment adds in understanding possible effects of these compounds. Science journalists are pivotal players in this respect. The public needs journalists that do not blow up small accidents to huge proportions but requires journalists that bring the touch of nuance in news. Politicians should realize that regulation by itself does not eliminate risk.

And scientists should remain seeking the academic debate. They should continue to admit that we still have limited knowledge on effects that can occur mostly in daily life, which is at a low-level exposure of compounds. That knowledge is growing, and fortunately not in a linear fashion but in much more exciting ways. We have shared a number of those exciting developments.

REFERENCES AND FURTHER READING

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