Chapter 7

"The Policy of Truth"—Anchoring Toxicology in Regulation

Lecturing on pharmacotherapy to medical students at the University of Maastricht is an enthralling task. During the fifth year of their study, the students follow an internship of several weeks at a practice of a family doctor. The students are asked to describe a case they encounter in which the patient receives polypharmacy treatment. The patient, frequently an elderly patient, receives multiple drugs for various diseases. The student is then requested to discuss the case with the supervising family doctor and the local pharmacist. Discussion on the action of the drugs, the choice for certain medication, the side effects, interactions between the drugs, and so on are subsequently debated between the students and the lecturer at the university. Indeed a fascinating task.

A frequently occurring observation is that the multitude of drugs may lead to what is known as "anticholinergic accumulation." It appears that many drugs inhibit the cholinergic system. This even holds for drugs without an evident anticholinergic action. Elderly people have a more fragile blood−brain barrier and the accumulation of these anticholinergic drugs in polypharmacy may lead to cognitive impairment. Drugs used for sleep, antiemetics, urinary incontinence, and also respiratory drugs, antidepressants, antipsychotics, and antiparkinson agents may add to this anticholinergic effect. Also over-the-counter, cold and flu remedies contribute to this effect. This seems to be a large problem in the steadily older growing population; however, no safety regulations seem applicable.

Toxicology and regulatory health and safety standards play a major role in the life of citizens of the Western World. Toxicology seems to be anchored in policymaking and regulation randomly. What kind of interaction takes place as to define, apply, and refine regulatory standards?

FROM TOXICOLOGY TO LEGISLATION

Articles on scientific failures always mention the example of thalidomide which is also known under several trade names like Softenon (in the

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Netherlands and Belgium) or Contergan (in Germany). The thalidomide disaster occurred in the 1950s. The sleeping and tranquilizing drug caused the birth of thousands of children with malformations.

After the introduction in the 1950s, thalidomide seemed a miracle drug. The sleeping drug was very effective in alleviating morning sickness in pregnant women. Moreover it seemed strikingly safe. It did not suppress breathing, something which was associated with older sleeping drugs.

Around 1960, some publications caused concern. The first report was that upon long-term use, the drug possibly caused nerve damage. Shortly after the introduction of thalidomide, the number of children with phocomelia increased, a severe condition in which the limbs of children were shortened or were even completely absent.

In Germany the drug was widely used. The Department of Pediatrics of the University of Hamburg did not have a single patient with phocomelia between 1949 and 1959. But in 1959, there was one patient; in 1960, 30; and in 1961, not less than 154 were identified. At that time, a smart German pediatrician, Dr. Lenz suspected a causal link between the use of thalidomide by pregnant women and the occurrence of phocomelia. It appeared that the use of the drug by the mother between the third and eighth week of pregnancy caused the damage (Fig. 7.1).

Further research learned that the teratogenic effect only occurred in some animal species. It was found that in some rabbit species the effect was seen when the compound was administered between the eighth and sixteenth day of pregnancy whereas mice did not show this effect at all.

This thalidomide tragedy led to the US Kefauver Harris Amendment or "Drug Efficacy Amendment" which is a 1962 amendment to the Federal

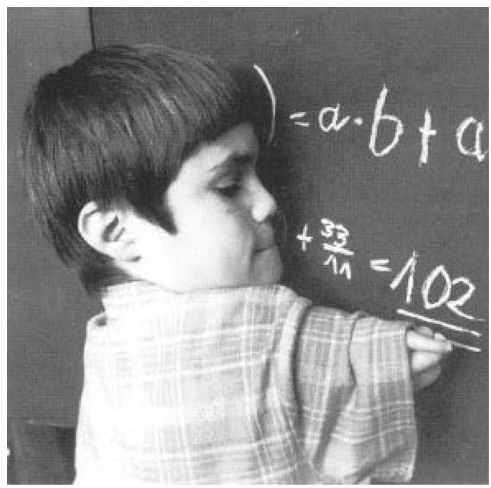

FIGURE 7.1 Photo of child with phocomelia. *The image used from "The Horror and Hope of Thalidomide." As published in www.chm.bris.ac.uk/motm/thalidomide/effects.html.*

Food, Drug, and Cosmetic Act. From that time onward, drug manufacturers were required to provide proof of the effectiveness *and* safety of drugs before approval. Also in Europe, the first European pharmaceutical directive (Directive 65/65/EEC, which dates from January 1965) was a reaction to the thalidomide tragedy and harmonized standards for authorization on approval of proprietary medicinal products. Teratogenic potential of a new drug was from that time on tested in at least three different animal species.

In this way was the toxicological finding leading in defining regulation. Sadly, some years ago the toxicity of thalidomide in babies was observed again in Brazil. In this case the "miracle drug" was administered to elderly woman to treat their leprosy. It appeared to be effective and the mothers conveniently passed the drug on to their daughters. Unaware of the dangers, pregnancy in some instances tragically resulted in phocomelia.

Interestingly, the drug has recently found new applications in the lung disease sarcoidosis and also in the treatment of cancer where it inhibits the sprouting of blood vessels (the angiogenesis) in the solid tumor. The severity of the problem warranted and in fact received political and regulatory actions.

However, even after these regulations, new problems arose indicating the necessity to be really cautious in administering drugs to pregnant women. Diethylstilbesterol (DES) is a synthetic nonsteroidal estrogen which was prescribed to women who has one or more miscarriages hoping to prevent those miscarriages. Although the effect was very doubtful, physicians remained prescribing DES until at least 1971. At that time it was recognized that in utero DES exposure of daughters of women who took the drug had a high chance of developing cancer of the vagina and cervix.

In 1971 the US Food and Drug Administration made a public warning on the use of DES by pregnant women. Unfortunately various countries in Europe continued the use of DES until the early 1980s. The DES daughters acquired more problems, like distortions of the uterus, lack of fertility, more vaginal discharge, and delivering more breech babies. The DES mothers between the age of 45 and 65 had a higher chance of breast cancer. In the Netherlands for example it was prescribed between 1947 and even until 1976. Amazing and regrettable that it took so long before the evident toxicological warnings were taken seriously. Learning of mistakes remains difficult.

What certainly remains is deep caution with regard to prescribing drugs to pregnant woman. It is also realized that many dietary ingredients are not safe for pregnant woman (Fig. 7.2).

FROM LEGISLATION TO TOXICOLOGY

More frequently, the reverse occurs, namely legislation dictates the toxicological approach that should be used. A recent example is the novel foods legislation. In many countries around the world, guidance documents have been published on the safety assessment on novel foods. A novel food should

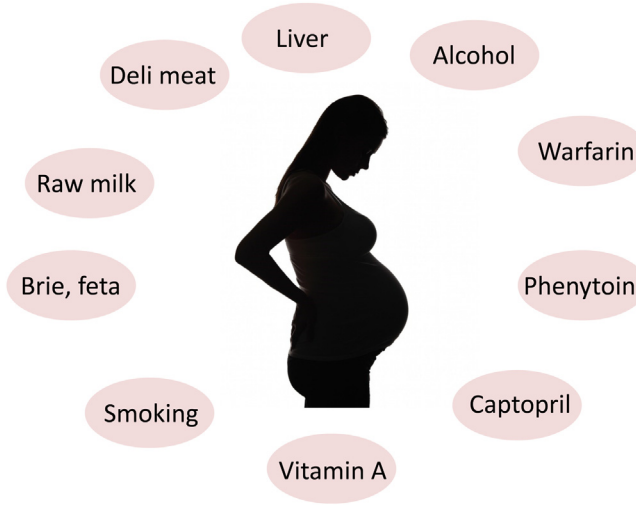

FIGURE 7.2 List of food, food derived ingredients, and drugs not safe for pregnant women.

be safe to consume and well labeled not to mislead consumers. The traditional approach for compounds is setting an acceptable daily intake (ADI) that entails a 100-fold safety margin when compared with the lowest no observable adverse effect level (NOAEL) in animals. This routine is not feasible for most novel foods which are complex in nature (Chapter 5: From Prevention to Precaution—Valuing Risks).

In the European Union it has been attempted to harmonize the authorization and use of novel foods and food ingredients since 1997 when the Regulation (EC) No. 258/97 on novel food and novel food ingredients was adopted. Novel food is defined as any food not consumed by humans within the European Union to a significant degree prior to May 15, 1997. It can be food with a new intentionally modified molecular structure. Food consisting of, isolated from, or produced from microorganisms, fungi, or algae, or from material of mineral origin, or food from cell culture or tissue, culture from animals or plants, and so on.

The regulation was further amended and lastly in 2015 in Regulation (EU) No. 2015/2283. The regulation will come into effect in January 2018. The European Food Safety Authority (EFSA) involved the various stakeholders via public consultation in finalizing the guidance documents. Quite some information has to be delivered (Fig. 7.3).

Besides information on the biological source, quantitative and qualitative data on the composition and possible impurities should also be provided. Hazards that may arise during packaging or storage should be identified. Proposed use and anticipated intake should be described. The toxicological information that should be provided includes a battery of in vitro tests to

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REGULATION (EU) 2015/2283 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of 25 November 2015

on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001

FIGURE 7.3 Front page of the Novel Food Regulation.

check for genotoxicity. In case of a positive result, in vivo studies should follow, e.g., a 90-day repeated dose toxicity study checking for neurotoxic, immunological, reproductive organ, or endocrine-mediated effects. The outcome of this subchronic toxicity study might form the trigger for a chronic toxicity or carcinogenicity study. In human toxicity studies, physical examination, studies on blood chemistry, urine analysis, blood pressure, and organ function tests may follow. In case the novel food exerts the so-called pharmacodynamics effects, specific studies may be required to ensure the novel food does not raise any safety concerns.

Explanations about the Novel Regulation in guidance documents describe simple and rather outdated toxicological methodology to ensure the safety. Novel techniques and notions about toxicology are not suggested. Why is the regulatory authority old-fashioned? Does it offer more security? Is the Novel Food regulation necessary because an immense toxicological problem exists or does it sprout from a general public sense of danger? Does society demand an extensive safety regulation? Obviously, our reflections on precautionary culture do give some pointers to answer such questions.

SOME TOXIC LIMITS SEEM TO BE CARVED IN STONE

Once limits of some sort have been established, it seems that these values sometimes firmly remain set and cannot be modified easily. New convincing knowledge will not always readily lead to change of threshold concentrations. An interesting example is nitrate.

Nitrate in drinking water has for decades been thought to be the cause of which is called the "blue baby syndrome," infantile methemoglobinemia. Nitrate changes the hemoglobin (the transporter of oxygen in the red blood cells) via the reduced form of nitrate, nitrite, into methemoglobin, a state of hemoglobin in which the iron is oxidized and is in the Fe^{3+} form which is unable to deliver oxygen to tissues. Transport of oxygen becomes hampered and a shortage of oxygen, cyanosis, leads to the bluish color of the intoxicated young child.

This general belief was fueled by the notion that infants under 6 months of age have a higher vulnerability for methemoglobin compared to adults because of lower enzyme activity to reduce the methemoglobin thus

restoring the oxygen transport in the first months of life. Because victims of methemoglobinemia showed to have drunk nitrate containing well water, nitrate was blamed for this effect. Moreover it was known that nitrite is more toxic for hemoglobin than nitrate and even children that did not drink nitrate contaminated water belonged to the victims.

That led to the suggestion that a bacterial infection in the gastrointestinal tract might be involved in the conversion of nitrate to nitrite, which was the ultimate cause of the toxicity. It led to a strict regulation for nitrate in drinking water. The World Health Organization (WHO) established a maximum level of 50 mg/L of nitrate in drinking water. This had huge consequences in rural areas where nitrate in soil water exists as a consequence of the use of nitrate containing fertilizers. A stream of reports followed indicating that even infants, without exposure to high-nitrate drinking water but with symptoms of diarrhea, could suffer from methemoglobinemia. Suggestions to reexamine the strict WHO maximum levels because diarrhea appeared a causative role in methemoglobinemia were largely neglected.

It was subsequently found that in response to colonic inflammation several tissues produced nitric oxide (NO) via an enzyme called nitric oxide synthase. The NO oxidizes to nitrite and nitrate. Endogenously formed NO may thus eventually result in the methemoglobinemia observed in young children as a result of drinking bacterial contaminated water. It was for a long time thought that it was the combination of bacterial contamination and nitrate which could lead to methemoglobinemia.

Despite persistent regulatory and scientific focus on the risks of exposure to nitrate, new scientific perspectives emerged once NO was discovered to be a major physiological chemical component. This discovery created a multifaceted image on the role of nitrate, but also nitrite, in human physiology. NO production has been shown to be vital to maintain normal blood circulation and defense against infection. NO, subsequently, is oxidized via nitrite to nitrate, which is conserved by the kidneys and concentrated in the saliva. The discovery of NO as a vital physiological chemical explains the common knowledge that mammals produce nitrate de novo. Mayerhofer already observed this as early as 1913. Infections yield the most noticeable instance of nitrate biosynthesis, explaining methemoglobinemia as a result of intestinal infections that reduce nitrate to the deleterious nitrite, and not exposure to exogenous nitrate as such.

It is now recognized that nitrate may even have beneficial effects because it can be reduced (e.g., by mouth and intestinal bacteria) into NO which may lead to decrease in blood pressure. Nitrate-rich vegetables may thus have a beneficial effect on blood pressure. It is amazing how a compound-like nitrate changes its face from extremely toxic to health promoting. The health limits, though, remain the same, indeed carved in stone it seems. Apparently it is very difficult to change existing views based on new facts about certain chemical compounds such as nitrate.

WHAT DETERMINES THE CHOICE OF TOPICS FOR TOXICOLOGICAL REGULATIONS?

A major determinant leading for human behavior is fear. Plain fear. Fear is an important regulator of our peripheral autonomic nervous system. The autonomic nervous system controls the function of our internal organs and acts largely unconsciously on for example the heart, respiration, and digestion. The autonomic nervous system can be divided into two branches—the sympathetic and the parasympathetic nervous system. The sympathetic branch is accountable for the flight−fright−fight response, while the parasympathetic nervous system is regarded as the rest−digest responsible branch. The nerves involved in the rapid excitatory sympathetic system are intensely interconnected which leads to a rapid overwhelming primary flight−fright−fight response. This response has to be quick because survival depends on it.

Fear elicits this response, action is needed, and a thoughtless reflex response is provoked. Fear is a main human driver and it is easy to envision that perceived toxicity leads to sympathetic preparedness to request toxicological regulation. This is very much in line with precautionary culture we discussed earlier. Indeed, historian Joanna Bourke observed: "fear of crime was not the most potent dogging late 20th century societies. There was another category of danger that frightened many Britons and Americans as the century staggered to its conclusion: ecological degradation." Part of that ecological degradation is deemed to be related to industrially produced synthetic chemicals.

Another factor that stimulates the quest for politicians and regulators to react on sometimes relatively small toxicological problems is the currently rapid communication. Small accidents are enlarged by the rapid communication. An occurrence in a distant location in the world is news within minutes. The consumer receives all kinds of information rapidly from different channels and asks for action.

Moreover, messages on toxicities keep on circulating. The proverbial "tomorrow's fish which is wrapped up in today's newspaper" is not valid anymore. Bad news, and unfortunately most news is bad, remains visible on the World Wide Web. It will further enlarge toxicologically cultured mishaps.

The feeling that (putative) large calamities are not dealt with properly by the authorities will easily give rise to conspiracy theories. Food scares are blown up to astronomical proportions and the emotion that responsible authorities do not act appropriately persists.

Contradictory, the fact that all the information is available nowadays generates the situation that only a small part of it can actually be read. It is just impossible to read the vast pile of literature (see also Chapter 8: Knowledge vs Insight). The consequence is that a selection is made of the all blogs, vlogs, articles, etc., someone will see and read. This selection is easily made within one's framework: those outings that are pleasing to the reader, i.e., notions that fit in one's own line of thinking will preferably be absorbed.

This is also known as confirmation bias. Concepts and views that are not in harmony with one's belief can easily be disregarded.

Other confirmation biases are formed by search engines like Google or Yahoo. Once you requested information on a certain toxicological problem, Google provides you with suggestions for novel selections along the same lines. In this way the natural propensity to most value information that confirms own ideas becomes reinforced. It becomes increasingly difficult to objectively obtain insights, which enable well-balanced legislative structures. Thus, legislation and regulation that leave enough freedom to research and innovation but at the same time fill in the gaps is needed. How do we protect the patient from cognitive impairment that may occur from polypharmacy (*vide supra*)?

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