Introduction

Objective of the Book. The objective of this book is to give full explanations of the meaning and usage of key toxicological terms. This requires a description of the underlying concepts, going well beyond a normal dictionary definition, making plain underlying assumptions and implications, especially for regulatory toxicology, which has come to influence so much of our life where the use of chemicals is concerned. There are many reasons for this. Firstly, with the advent of antibiotics and the development of increasingly effective means of controlling infectious disease, attention was turned to diseases resulting from exposure to chemicals. Prevention of these diseases required regulation of exposure and so new laws, such as the Toxic Substances Control Act in the USA, were introduced. These laws required assessment of toxicity and legally defined definitions of what constituted toxicity. Thus, for example, the terms 'toxic' and 'very toxic' have been given quantitative definitions based on the LD_{50} in order that that substances can be labelled with these terms to provide some warning of danger for potential users. Of course, the older, less quantitative and more generalized usage has continued. This can lead to misunderstandings that may have serious consequences. For example, substances that are not labelled as 'toxic' may be assumed to be non-toxic and consequently used carelessly, with disastrous results. This is because the LD_{50}, the historic basis in law for classification as 'toxic', is, at best, an indication of the ability of a substance to cause death following short-term exposure. It tells us nothing about lethality of long-term exposure, probably a very common situation in the human context, or about other toxic effects that may be severely disabling but not immediately lethal.

Results of Misunderstanding of Concepts. The possible harmful effects of misunderstood toxicological terms on human health are fairly obvious to most people but the economic consequences tend to receive less attention by the general public. In Europe, the main driving force for development of

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By John H Duffus, Douglas M Templeton and Monica Nordberg

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regulatory toxicology has been trade. It was already clear in the 1960s that trade in chemicals was being hindered by the variety of regulatory systems and hazard (toxicity) classifications applied in different countries around the world. This was an immediate problem for European nations seeking to establish free trade within the growing European Community, now the European Union (EU). The result was the 7th amendment to the Directive on Classification, Packaging and Labelling, that applied a common approach to toxicity assessment and subsequent labelling for all members of the European Community. Since most substances in commercial use had not been tested for toxicity, this was the start of a demand for toxicity testing that led subsequently to the Notification of New Substances Directive and which has culminated in the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) Regulation that came into effect in 2008. This Regulation has made risk evaluation for toxicity and other hazards compulsory for all substances in use within the European Union. If acceptable, the substance will be authorized for marketing throughout the European Union. Without such authorization marketing is prohibited. The methods to be applied for toxicity testing and evaluation are described in detail in Technical Guidance Documents to ensure that the regulatory authorities in all the EU countries apply the same criteria and reach the same conclusions. This helps to ensure that trade is not impeded by contrary evaluations in the different countries of the EU. The downside is that any toxicological errors in the evaluation procedures are very difficult to change because of the inertia inevitable in such a system. Thus, erroneous evaluations can have a long-term effect on the availability of substances of value and may even result in the substitution of authorized toxic substances for less toxic alternatives that have not been authorized because the original evaluation was based on inadequate toxicology. REACH is available online at: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:354:0060:0061%20:EN:PDF>.

The successor to REACH as state-of-the-art legislation is likely to be the Globally Harmonized System of Classification and Labelling of Chemicals (GHS), which is being developed by United Nations (UN) as a system to be adopted worldwide. The UN GHS is not a formal treaty, but instead is a non-legally binding international agreement. Therefore, countries (or trading blocks) must create local or national legislation to implement the GHS. The Organization for Economic Cooperation and Development (OECD) is developing proposals for classification criteria and labelling in the area of health and environmental hazards, at the request of the UN Sub-Committee of Experts on the GHS. A Task Force on Harmonization of Classification and Labelling has been established to coordinate the technical work carried out by the experts. The involvement of the OECD shows the importance that concepts in toxicology now have for world trade. An early and valuable consequence of this was the investment by the countries belonging to OECD of large amounts money to fund the development of Guidelines for Testing of Chemicals (including toxicity tests). These are now the 'gold standard' for toxicity tests and, where applied precisely as described, provide data that are accepted

worldwide as the basis for decisions on risk management of chemicals in use. An important part of this has been the requirement for good laboratory practice and quality assurance. The current draft of GHS is available online at: http://www.unece.org/trans/danger/publi/ghs/ghs_rev02/02files_e.html. The current draft of the OECD Guidelines for Testing of Chemicals is available online at: <http://www.oecd.org/document_22/0,3343,en_2649_34377_1916054_1_1_1_1,00.html>.

In the negotiations for improved international understanding of chemical safety matters and implementation of harmonized laws, linguistic barriers lead to problems between nations and even between scientific disciplines in terms of comprehension and, therefore, in reaching agreement. This leads to considerable time being wasted at meetings in reaching a common perception of the nature and significance of problems and, hence, to difficulties in achieving a final agreement on acceptable solutions. The time that is wasted is also a waste of the money invested in the meeting and a waste of the valuable time of the participants. Hopefully, this book may help to reduce such waste.

Another consequence of misunderstood concepts in toxicology is misclassification of important substances, either prohibiting their use unnecessarily or permitting their use when the risk involved should have been perceived and avoided. A widely misunderstood concept has been 'chemical speciation'. This concept is tacitly assumed for organic substances, which are all chemical species of carbon. Carbon compounds have never been given blanket toxicity classification on the basis of carbon being the main element present and, thus, fundamental to their structure. There is no subset of toxicology called 'carbon toxicology', whereas there is a subset called 'metal toxicology', even though different chemical species of metals have vastly different properties, just as carbon compounds do. The consequence of this misunderstanding of chemistry has been blanket classification of, for example, all nickel compounds as carcinogens, in the absence of evidence relating to most of the compounds, on the assumption that nickel cations will be released from all such compounds and that hydrated nickel cations are carcinogenic. There is little evidence to support this contention in spite of many related studies. As one might expect, there is no report of nickel alloys in any form, including stainless steel, coinage, dental and other surgical prosthetics, or even jewellery such as ear rings in intimate contact with the human body, having caused cancer, although allergic reactions have been reported for the last mentioned. By contrast, the most acutely toxic form of nickel is a gas, nickel tetracarbonyl, which is probably fatal through its carbonyl groups and not through the nickel atom, even if it does eventually release a free cation. Whether nickel tetracarbonyl is ever carcinogenic is a matter of dispute.