Regulatory Toxicology and Pharmacology 82 (2016) 158–166

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Commentary

Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society

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ARTICLE INFO

Article history:
Received 13 October 2016
Received in revised form
20 October 2016
Accepted 21 October 2016
Available online 22 October 2016

Keywords:
Classification
Hazard characterization
Risk assessment
Carcinogenicity
IARC
GHS

ABSTRACT

Classification schemes for carcinogenicity based solely on hazard-identification such as the IARC monograph process and the UN system adopted in the EU have become outmoded. They are based on a concept developed in the 1970s that chemicals could be divided into two classes: carcinogens and non-carcinogens. Categorization in this way places into the same category chemicals and agents with widely differing potencies and modes of action. This is how eating processed meat can fall into the same category as sulfur mustard gas. Approaches based on hazard and risk characterization present an integrated and balanced picture of hazard, dose response and exposure and allow informed risk management decisions to be taken. Because a risk-based decision framework fully considers hazard in the context of dose, potency, and exposure the unintended downsides of a hazard only approach are avoided, e.g., health scares, unnecessary economic costs, loss of beneficial products, adoption of strategies with greater health costs, and the diversion of public funds into unnecessary research. An initiative to agree upon a standardized, internationally acceptable methodology for carcinogen assessment is needed now. The approach should incorporate principles and concepts of existing international consensus-based frameworks including the WHO IPCS mode of action framework.

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1. Introduction

Cancer prevention is the primary objective of the evaluation of chemicals for their human carcinogenicity potential. This objective, however, is undermined by confusion resulting from conflicting pronouncements coming from multiple international and national agencies (Guardian, 2016). This has led to carcinogen definition and regulation being called “the poor relation to other cancer preventative measures” (Lancet, 2016). The problem arises from the different concepts and approaches that are being used, some of

Abbreviations: ACGIH, American Conference of Government Industrial Hygienists; CoC, United Kingdom Committee on Carcinogenicity; ECHA, European Chemicals Agency; EFSA, European Food Safety Authority; EPA, United States Environmental Protection Agency; EU, European Union; GHS, United Nations Global Harmonized System for Classification and Labelling; IARC, International Agency for Research on Cancer; IPCS, International Programme on Chemical Safety; JMPR, Joint FAO/WHO Meeting on Pesticide Residues; MOA, Mode of Action; NCI, United States National Cancer Institute; PMRA, Health Canada Pest Management Regulatory Agency; WHO, World Health Organization.

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http://dx.doi.org/10.1016/j.yrtph.2016.10.014
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which were developed half a century ago. Their appropriateness was questionable at the time and they have now clearly become out of step with advances in scientific understanding and modern regulatory science.

Classifying chemicals on hazard-identification alone is one such outmoded concept. The International Agency for Research on Cancer (IARC) classification process for carcinogenicity and the United Nations Global Harmonized System for Classification and Labelling (GHS) (adapted and adopted in the EU and elsewhere) processes for carcinogenicity (and reproductive toxicity) are based on this outmoded concept.

The original intention of these processes was to raise a warning flag for chemicals of potential concern which would lead to fuller evaluation to determine if risk management measures need to be taken. However, the warning flags are never removed, and sometimes they even appear after more complete evaluation by regulatory authorities has determined that adequate risk management is in place. Of even greater concern is that evaluation often stops at classification and acceptability is based only on hazard with no consideration of the potential risk under even extreme (though remotely possible) human exposure.

This hazard-identification only process places chemicals with widely differing potencies and very different modes of action into the same category. Processed meat (consumption) and sulfur mustard gas are placed into the same category (group 1) by IARC as described in section 6. This leads to confusion; should we treat processed meat as we do sulfur mustard gas – reduce exposure to zero; or should we treat sulfur mustard gas as we do red meat – consider it part of a healthy life style in moderation? This categorization can thus lead to unnecessary public anxiety; resources may be diverted that would be better used addressing more substantial problems; safe and useful products come under unnecessary and excessive scrutiny; and they may even be replaced by other less characterized and potentially less safe products.

This present work describes the origins of classification schemes based on hazard-identification, acknowledges that they were once useful, explains why they no longer serve a useful role and illustrates how science-based approaches in a risk based decision framework are more suited to protecting human health in the 21st century.

2. Advances in public health and chemical risk management

The 20th century saw great advances in the state of public health; managing the potential risks from chemicals has played its part. Life expectancy increased by over 30 years in Europe and the Americas between 1900 and 2000 (Roser, 2015). Certain chemicals and technologies developed in the late 19th century and early 20th century did come at a price, however. At the time, there was poor understanding of the range of biological effects that chemicals could cause until the pioneering observational studies that identified how chemicals could adversely affect human health were published (Goldblatt, 1944). Many adverse effects observed in humans were then verified in animal studies. By the middle of the 20th century there was a shift towards the use of animal studies to predict what could happen in humans, which led, in the 60's and 70's, to the development of extensive and diverse toxicological studies to identify and characterize chemical hazards, and predict the human safe dose, before adverse effects could occur in humans. Hazard-identification and characterization via animal studies became the standard for predicting and then avoiding potential adverse effects in humans. As a result of this approach to chemical safety assessment, exposure to high-risk chemicals has been progressively reduced (Kauppinen et al., 2013). Whilst not perfect, this approach has the advantage that chemicals potentially toxic to humans are identified before there is any human exposure.

3. Classification and risk assessment

The results of laboratory animal toxicology studies are used for identifying in animals adverse health effects assumed without additional information to represent a potential hazard to humans which may be further characterized in terms of severity and dose response. This information is then most appropriately used for assessing potential human health impact from the use or presence in the environment of the chemical. There are two major ways in which this is done: risk assessment and classification.

Risk assessment requires estimation of the human exposure in terms of duration, frequency and magnitude to derive a plausible maximum dose to which humans might be exposed. This dose is then compared with the projected safe human dose level derived from hazard characterization; if the projected exposure is lower than the projected human safe dose then safety in use can be assumed, and if not then it may be necessary to identify and implement risk mitigation measures. Risk assessment also requires evaluation of the relevance of the findings at high doses in animal studies to lower exposures in humans. Mechanisms leading to toxicity in animals might not be relevant to humans, or changes occurring at high doses might not be relevant to low does. In other words, scientific evaluations are necessary.

Classification uses a different approach while being based on similar principles. It focuses on the hazard which has been identified, usually from animal studies and, then, grades the hazard into various categories based on the severity and, in some instances, dose response. Classification was originally intended to provide information on the effects of a chemical following acute exposure for labelling purposes for transport (UN, 2011). However, its use has broadened substantially so that many regulatory schemes are based solely on classification for a range of end points following either acute or repeated exposure leading directly to risk management action without consideration of the chemical potency, severity of the effect or mode of action or the nature and extent of human exposure.

4. Problems with classification

The advantages and disadvantages of both approaches have been reviewed by Barlow et al., 2015, who concluded that both approaches have their uses depending on the situation being addressed. Classification is more appropriate for acute toxicity or in situations where it is hypothesized that there is no threshold for an adverse effect. It requires less data and can be valuable in providing guidance when a decision has to be taken before a full evaluation has been carried out. Risk assessment provides more information and insight into the magnitude of risks, and can be used as a basis for deriving “safe” levels of exposure. However, problems can arise when both approaches are used in regulation by the same or different agencies that address the same agent/substance. This separation of decision-making can result in hazard-based restrictions on marketing and use or unnecessary remediation of environmental levels, even when risk-based assessments show there is reasonable certainty no harm will result. This in turn can lead to contradictory, confusing and ultimately unnecessary actions.

These problems arise most often when the classification process focuses simply on identifying the hazard but does not go on to characterize the hazard in terms of severity, dose response and mode of action. This is the situation with some schemes in the areas of carcinogenicity, and reproductive toxicity, and it is a source of the current controversy on how to prioritise and manage the risk posed

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