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Regulatory Toxicology and Pharmacology xxx (2016) 1–9

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 xxx

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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Please cite this article in press as: Boobis, A.R., et al., Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society, Regulatory Toxicology and Pharmacology (2016), 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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by chemicals identified as endocrine disrupters. The omission of characterization of both hazard and risk in these schemes stems from the historical special treatment given to certain health effects based on their public perception (Slovic, 1987) such as carcinogenic and reproductive toxicity effects, and more recently endocrine disruption, neurotoxicity and immunotoxicity.

5. Cancer as a major concern

Cancer had become such a concern that in 1971 US President Nixon signed the National Cancer Act saying in his State of the Union Address "The time has come when the same type of concentrated effort that split the atom and took a man to the moon should be turned toward conquering this dread disease". Large sums of money were devoted to reducing cancer deaths and prevention was seen as part of the "war on cancer" as well as the discovery and development of treatments. It was believed, at the time, that a large proportion of cancers were caused by industrial chemicals. Hueper (1955) from the National Cancer Institute (NCI) had concluded that cancer from exposure to industrial chemicals was of far greater concern than cancer from tobacco smoking. This has since been shown to be incorrect as tobacco smoking is now recognized as the second leading cause of death globally, with 6.3 million deaths annually attributed to smoking (GBD2010, 2012).

In the middle of the 20th century, the concept developed that chemicals could be segregated into two classes: carcinogens and non-carcinogens. It was postulated that a major reduction in cancer incidence would result if we could identify the "carcinogens" and, hence, replace them with "non-carcinogens". This concept started the drive towards using hazard-identification alone for carcinogenicity which has continued for nearly half a century in a largely unmodified way. It was also the basis for the use of the Maximum Tolerated Dose in animal studies which was thought to optimize the chances of identifying "carcinogens". Whilst the concept was considered sound in principle at the time, it was based on a fundamental misconception. There is now a greater understanding of the complex biology and etiology of cancer, specifically how chemical exposure can lead to cancer, and the idea of a binary separation into "carcinogens" and "non-carcinogens" has proved to be overly simplistic. Indeed, a very wide range of chemical cans cause cancer under the "right" experimental circumstances many of which having no relevance to humans or achievable exposure levels (see section 7).

6. Cancer classification

Carcinogen hazard-identification is primarily based on the evaluation of human epidemiological data, if available, and the results of long term bioassays in laboratory rodents. At first most of the evaluations were based upon human epidemiology studies in occupational settings. Processes were set up by several national and international bodies to identify carcinogens that were largely based on Sir Austin Bradford Hill's considerations for causality (Hill, 1965). The strength of the evidence for causality varied and, therefore, it was graded to allow chemicals to be placed into different categories regarding the confidence in a causal link for carcinogenicity in humans.

The categories used today by IARC (2012) still reflect this:

- Group 1: The agent is *carcinogenic to humans*
- Group 2A: The agent is *probably carcinogenic to humans*
- Group 2B: The agent is *possibly carcinogenic to humans.*
- Group 3: The agent is *not classifiable as to its carcinogenicity to humans*
- Group 4: The agent is *probably not carcinogenic to humans.*

Whether by accident or design, this was a classification system and, therefore, it was not surprising that this system was co-opted into some of the chemical classification schemes which were emerging in the 1970s and 1980s. However, unlike the other classification systems developed for health protection, the carcinogenicity scheme deliberately avoided the valuable context of hazard or of dose response, severity, and mode of action or exposure. At the time this scheme was put in place, such characterization was not thought necessary as the aim was simply to identify "carcinogens" and to eliminate them.

The EU in its Classification and Labelling Guidelines (ECHA, 2012) has implemented the UN GHS categorization system which is very similar using strength of evidence involving only the enumeration of tumors in human and animal studies and determination of their level of statistical significance. The Guidelines state that "*Sufficient human evidence demonstrates causality between human exposure and the development of cancer, whereas sufficient evidence in animals shows a causal relationship between the substance and an increased incidence of tumors. Limited evidence in humans is demonstrated by a positive association between exposure and cancer, but a causal relationship cannot be stated. Limited evidence in animals is provided when data suggest a carcinogenic effect, but are less than sufficient. The terms 'sufficient' and 'limited' have been used here as they have been defined by the International Agency for Research on Cancer (IARC).*"

The UN GHS categories are.

- Category 1A: Known to have carcinogenic potential for humans, the placing of a substance in this category is largely based on human evidence
- Category 1B: Presumed to have carcinogenic potential for humans: the placing of a substance in this category is largely based on animal evidence
- Category 2: Suspected Human carcinogen

Thus a system set up half a century ago based on an overly simplistic concept as an initial attempt to address the disease burden of cancer has found its way into classification schemes for chemicals and also into some downstream risk management processes. The consequences may not have been intended but they were predictable. The pressure to replace a chemical which had been identified as a potential human carcinogen was immense, even on the basis of animal studies, and the very act of categorizing a chemical in this way leads to a stigma which would often result in major changes in its use, including withdrawal, whereas risk-based assessments show that there is reasonable certainty no harm will result from its use.

7. Introduction of the cancer bioassay

All of this was occurring at the time as the potential of chemicals to cause adverse effects was being recognized and animal models were being developed. The long term bioassay for carcinogenicity was accepted as an OECD guideline study in 1981 (OECD, 2009) and the results of rodent bioassays were used as evidence, either alongside or instead of epidemiology, in deciding whether a chemical should be classified as a "carcinogen". Since known human carcinogens, based on epidemiology studies, also caused cancer in animal models, it was concluded that a chemical that caused cancer in an animal model must also cause cancer in humans. Their reverse incorrect logic has been proven wrong numerous times. For example, about 60% of pharmaceuticals tested in the rodent bioassay gave positive results, but have been deemed safe for human use (Brambilla et al., 2012). Applying a hazard classification would have kept these life-saving pharmaceuticals off

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the market, including statins and proton pump inhibitors, two of the most widely used classes of drugs today.

The bioassay was intended for hazard-identification and was therefore designed to maximize the ability to detect "carcinogenicity". Dosing was for as much of the life time of the animals as possible. Historically, exposure started after weaning, some newer study designs start exposure before birth. The highest dose was set as a Minimally Toxic Dose that would not impact the animals' normal lifespan from effects other than cancer. This evolved into the Maximum Tolerated Dose (MTD), which increased the doses used in an attempt to increase sensitivity to detect the "carcinogenicity" of low potency compounds. Under these assay conditions 50% of chemicals, both synthetic and natural, were capable of increasing the incidence of neoplasms (both malignant and benign) (Gold et al., 1989). Numerous studies have shown that as the experimental dose of a chemical is increased, different saturable or inducible toxicokinetic (e.g., metabolism, uptake, excretion) and toxicodynamic (e.g., homeostasis, receptor interactions, protein binding, repair mechanisms) processes involved in chemical toxicity (e.g., tumorigenicity) can be involved, which may not be engaged at environmental exposures (Slikker et al., 2004a,b). It seems that the high doses used were triggering different mechanisms which lead to the development of neoplasms in laboratory animals. Determining which mechanisms are operative along the dose-response curve has important implications for interpreting bioassay data for the purposes of predicting human risk.

The classification processes were, therefore, adapted to include the results of the animal bioassays in determining the strength of evidence for carcinogenicity. Induction of excess neoplasms in rodents, irrespective of the dose, was taken as strong evidence for carcinogenicity in humans and chemicals were categorized accordingly. The large proportion of chemicals classified in this way led to questioning of the validity of the assays and the overall process (Ames and Gold, 1990). The finding that around 50% of chemicals caused neoplasms in these assays undermines the concept of separating chemicals into "carcinogens" and "non-carcinogens". It is not logical that half the chemicals in use cause cancer in humans particularly given the high experimental doses used and the high incidence of background tumors in certain rodent species and strains and the lack of confirmation in scores of human epidemiology studies (Pastoor and Stevens, 2005).

8. Increasing understanding of carcinogenicity (and its impact on risk assessment and management)

Increasing understanding of chemically-driven carcinogenic pathways over the last several decades has progressively raised questions regarding the relevance for human health of certain tumor findings in rodent bioassays. Given the issues and debates around the human relevance and dose response of rodent tumors, advances in knowledge of chemical carcinogenesis, and emerging cost and time-effective methods to investigate modes of action (MOAs), the international need for harmonized guidance on how to look at mode of action information in cancer assessment was recognized. Work under the auspices of the WHO International Programme for Chemical Safety (IPCS) began in the 1990's to develop a weight of evidence framework (Sonich-Mullin et al., 2001). In the first stage of the framework one determines whether it is possible to establish an MOA for the animal tumor(s) under investigation by identifying a series of key events along the causal pathway to cancer using a weight-of-evidence approach based on the Bradford Hill considerations. The key events are compared first qualitatively and then quantitatively between those which would occur in the experimental animals and those which would occur in humans. Finally, a clear statement of confidence, analysis, and implications for risk assessment is produced.

The resulting IPCS mode of action framework was an important development in moving cancer assessment away from a phenomenological approach and toward enabling the integration of a fuller biological understanding of how chemicals induce neoplasia and a better understanding of the dose response relationships. Shortly afterwards, the IPCS framework was expanded to address how MOA knowledge can be used to evaluate the human relevance of animal responses based on species concordance analyzes (Meek et al., 2003; Boobis et al., 2006). In the early mid 2000's, the approach was extended to evaluate non-cancer endpoints and life stage information (Boobis et al., 2008; Seed et al., 2005) and to incorporate the quantitative consideration of dose response (Julien et al., 2009; Simon et al., 2014). IPCS has now updated the framework to consolidate the international work that had been done and to emphasize that MoA analyzes should be problem formulation-based recognizing that MOA knowledge can inform different risk management decisions: priority setting, read across, or guiding research, not just for risk assessment where it has been most frequently used (Meek et al., 2014).

When using this approach for assessing carcinogenicity, there are three broad outcomes which have an impact on how the chemical should be further evaluated:

- Rodent carcinogens that are considered relevant for humans and which have mode(s) of action indicating that there is no presumption of a threshold for the dose response.
- Rodent carcinogens that are considered relevant for humans and which have a mode(s) of action indicating that there is a threshold for the dose response. These often result from modes of action associated with the high experimental treatment doses that result in secondary processes (e.g., sustained cytotoxicity and compensatory hyperplasia) where a no effect level or margin of safety can be established. A substantial number of chemicals have been shown to fall into this group including the pesticides acifluorfen sodium, amitrole, captan, cyproconazole, folpet, lactofen, and pyroxasulfone (EPA, 2015)
- Rodent carcinogens that are considered to have mode(s) of action not relevant for humans. A number of chemicals induce tumors by modes of action well documented to be non-relevant to humans. Some examples are: kidney tumors in male rats associated with substances causing α2u-globulin nephropathy; pheochromocytomas in male rats exposed to particulates through inhalation secondary to hypoxemia; Leydig cell adenomas induced by dopamine antagonists or gonadotropin-releasing hormone (GnRH); certain thyroid tumors in rodents mediated by UDP glucuronyltransferase (UGT) induction (listed in the Classification Guidelines by ECHA, 2012).

The process for the assessment of the carcinogenicity of chemicals by many regulatory authorities or organisations has incorporated the concept that different modes of action have different implications for human safety. Examples are:

8.1. US EPA

The US EPA (2005) revised their Cancer Risk Assessment Guidelines to bring in more relevant science in the cancer risk assessment process by incorporating a framework for analyzing mode of action (consistent with the WHO IPCS approach). The US EPA also replaced their cancer categories with descriptors and weight of evidence narratives, and to acknowledge that carcinogens should be considered in ways appropriate to their full hazard and risk characterization. In the absence of data, the US EPA takes a public health protective position that animal tumor findings are

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assumed to be relevant to humans, and cancer risks are assumed to conform with the default hypothesis of non-threshold, low dose linearity. However, sufficient, scientifically justifiable mode of action information can support different conclusions. Non-linear dose response modelling may be appropriate. In some cases, the animal tumors are concluded to be not relevant to humans and thus not to be used in human risk assessment. These considerations are reflected in the descriptors which the EPA applies. More than one descriptor can be used when an agent's effects differ by dose or exposure route. For example, an agent may be "Carcinogenic to Humans" by one exposure route but "Not Likely to Be Carcinogenic" by a route by which it is not absorbed. Also, an agent could be "Likely to Be Carcinogenic" above a specified dose but "Not Likely to Be Carcinogenic" below that dose because a key event in tumor formation does not occur below that dose. These are descriptors which enable the US EPA to apply the appropriate risk assessment methodology.

8.2. ACGIH

The American Conference of Government Industrial Hygienists (ACGIH, 2016) has developed categories which describe different classifications based on the concept that different modes of action have different implications for human safety:

- A1 – Confirmed human carcinogen
- A2 – Suspected human carcinogen
- A3 – Animal carcinogen. The agent is not likely to cause cancer in humans except under uncommon or unlikely routes or levels of exposure. The agent is carcinogenic in experimental animals at a relatively high dose, by route(s) of administration, at site(s), of histologic type(s), or by mechanism(s) that may not be relevant to worker exposure.
- A4 – Not classifiable as a human carcinogen
- A5 – Not suspected as a human carcinogen

8.3. UK CoC

The United Kingdom Committee on Carcinogenicity (CoC, 2012) developed a decision tree approach which takes into account the mode of action in the way the hazard is characterized and the risk assessed before risk management decisions are taken. The decision tree reviews the carcinogenicity data and leads to one of three conclusions:

- Exposure should be as low as reasonably possible for substances with a genotoxic mode of action
- Exposure should be below a level set using identification of critical end points and use of uncertainty factors for substances with other modes of action considered relevant to humans.
- Exposure should be below levels determined by consideration of non-carcinogenicity end-points for substances with modes of action for carcinogenicity considered non-relevant to humans.

8.4. SCOEL

The EU Scientific Committee on Occupational Exposure Limits (SCOEL) set criteria to include mode of action and strength of available data to provide input to the management of carcinogens (Bolt and Huici-Montagud, 2008):

A) Non-threshold genotoxic carcinogens; for low-dose assessment of risk, the linear non-threshold (LNT) model appears appropriate. For these chemicals, regulations (risk management) may be based on the ALARA principle ("as low as reasonably achievable"), technical feasibility, and other socio-political considerations.
B) Genotoxic carcinogens, for which the existence of a threshold cannot be sufficiently supported at present. In these cases, the LNT model may be used as a default assumption, based on the scientific uncertainty.
C) Genotoxic carcinogens with a practical threshold, as supported by studies on mechanisms and/or toxicokinetics; health-based exposure limits may be based on an established NOAEL (no observed adverse effect level).
D) Non-genotoxic carcinogens and non-DNA-reactive carcinogens; for these compounds a true ("perfect") threshold is associated with a clearly founded NOAEL.

Each of these modern schemes derives the dose which is predicted to be of concern, or not, in humans based on the concept that different modes of action have different implications for human safety.

9. Unchanged processes become outmoded

Although it has not modified its categories since 1971, IARC currently makes no claim that its role is anything other than hazard-identification; *"These categories refer only to the strength of the evidence that an exposure is carcinogenic and not to the extent of its carcinogenic activity (potency)."* (IARC, 2015a). However, on occasion, IARC has pronounced on the risk of some of the carcinogenic hazards that they have identified (IARC, 2015b).

The EU Classification and Labelling Guidelines (ECHA, 2012) uses a system based on the strength of evidence for hazard-identification as a "carcinogen". The guidelines allow for a chemical to be classified as not a carcinogen if a mode of action can be established to be not relevant to humans. However, for carcinogens that are considered relevant for humans, the system does not distinguish between those which have a mode of action indicating that there is a presumption of no threshold for the dose response and those which have a mode of action indicating that there is a threshold for the dose response.

Categorization of carcinogenicity of agents (e.g., commodity or pesticide chemicals, food additives, viruses, or natural products) by the strength of evidence (e.g., animal cancer bioassays, epidemiology, other experimental in vitro and in vivo) without consideration of mode of action, dose-response and human exposure can result in agents being placed into the same category that vary widely in their likelihood to cause cancer. It has been suggested that the EU GHS process could be improved by including potency in a weight of evidence approach using methods which are already part of the EU Classification, Labeling and Packaging guidelines relating to the presence of substances classified as carcinogens in mixtures and preparations (Hennes et al., 2014).

10. Problems resulting from use of outmoded processes

The problems caused by hazard-identification classification schemes are complex and they have consequences for many parts of society. The original intent of these schemes was to identify chemicals or other agents which may be of concern and thus require further evaluation including full risk assessments to determine if action would be needed to mitigate a risk. We see this process working in the strategy used by the EPA (EPA, 2005) and UK Committee on Carcinogenicity (CoC, 2012) where the initial hazard-identification as a carcinogen triggers a logical and scientific consideration of the risk to human health which takes into account

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the potency, the mode of action and the magnitude, duration, frequency and route of exposure. Appropriate risk mismanagement decisions can then be made which can range from taking no action, using personal protective equipment, decreasing personal exposure, restrictions on use, to outright banning of use in extreme circumstances.

However, all too often the public response to the classification by hazard-identification alone is not so reasoned. For example IARC classification as "carcinogenic to humans", "probably carcinogenic to humans" or "possibly carcinogenic to humans" can all lead to negative publicity and a "health scare". The "health scare" can trigger anxiety and lead to behavior which is detrimental to actually achieving desirable public health goals (Berry, 2016). Government and other agencies then have to use precious resources to respond because of publicly perceived rather than actual threats.

Several organisations have had to explain to the public what IARC does in attempts to alleviate unnecessary concern (Health Canada, 2016; Cancer Research UK, 2012). As an example, Cancer Research UK sums up what IARC does: *"Just because something is in IARC's top level category, it doesn't necessarily mean it's public health number one – it's more complex than that. IARC does 'hazard identification', not 'risk assessment'. That sounds quite technical, but what it means is that IARC isn't in the business of telling us how potent something is in causing cancer – only whether it does so or not. To take an analogy, think of banana skins. They definitely can cause accidents – but in practice this doesn't happen very often (unless you work in a banana factory). And the sort of harm you can come to from slipping on a banana skin isn't generally as severe as, say, being in a car accident. But under a hazard identification system like IARC's, 'banana skins' and 'cars' would come under the same category – they both definitely do cause accidents."*

Cancer Research UK (2012) explains that *"IARC categories are designed to flag things up to policy makers, so they can then analyse the scale of the problem, weigh the risks against the benefits, and bring in appropriate legislation."* IARC sometimes assesses chemicals after they have already been considered in detail for both potential hazard and risk by stringent agencies responsible for regulation, such as US EPA, EFSA, ECHA, JMPR, PMRA. This lack of coordination and co-operation can lead to problems, confusion, duplication of efforts, and the expenditure of unnecessary resources. A recent example of this has arisen with the herbicide glyphosate. The European Food Safety Authority has completed an extensive review of its original evaluation following a second mandate from the European Commission (EFSA, 2015) to consider the findings from IARC's classification of glyphosate as *"a probable human carcinogen"* (IARC, 2015a,b), They came to the conclusion that *"glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence does not support classification with regard to its carcinogenic potential"* (EFSA 2015). Oddly, IARC reviewers have chosen to dispute the findings of the EFSA process and criticize EFSA for "*an over-reliance on non-publicly available industry-provided studies using a limited set of assays that define the minimum data necessary for the marketing of a pesticide*" (Portier et al., 2015). In the case of pesticides, it is the legal responsibility of the regulated industry to provide all the studies needed to establish the safety of their products. Extensive data are legally mandated by regulatory authorities to enable them to evaluate efficacy and safety, and these data are generated in accordance with Good Laboratory Practice and a series of internationally harmonized and scientifically peer-reviewed study protocols, designed to maintain a high standard of scientific quality and consistency, and to provide confidence that study results are repeatable and acceptable. So it should not be surprising that there are large databases of studies sponsored by pesticides registrants given the legal and regulatory requirements by authorities, who have access to all the raw data. It is noteworthy that based on an weight of evidence approach that evaluates the consistency, dose response, time course, and biological plausibility of all relevant evidence, JMPR concluded that glyphosate *"is unlikely to pose a carcinogenic risk to humans from exposure through the diet"* (JMPR, 2016). EPA recently articulated its proposed conclusions that "*The strongest support is for "not likely to be carcinogenic to humans at doses relevant to human health risk assessment.""* (EPA, 2016).

The EU classification system can also cause problems because there are automatic risk management consequences built into downstream regulations. These are exemplified in the EU Directive on the regulation of crop protection products (EU, 2009). This regulation applies so-called cut off criteria which do not allow any products categorized as category 1A or 1B carcinogens to be registered for use. This is an example of a process where hazard-identification goes directly to risk management without going through hazard characterization and risk assessment, even though the regulations demand that a full toxicological and exposure data set be produced and a risk assessment be performed for every requested use. In many cases, a risk assessment using the modern approaches would show that different modes of action have different implications for human safety and would therefore impact the regulatory decision.

Chemicals and other agents, particularly those that are in widespread use that are flagged by classification processes based on hazard-identification alone tend to come under close scrutiny and become the subject of debate and concerted public campaigns. For instance the IARC classification of glyphosate has given rise to headlines such as "War in Europe- Battle over Glyphosate" (Genetic Literacy Project, 2016), "EU scientists in row over safety of Glyphosate weedkiller" Guardian (2016), and "How the World Health Organization's cancer agency confuses consumers" (Reuters, 2016). The listing of a chemical by these hazard-identification only based schemes can have major implications either because of downstream regulation or because of the reputational damage which can be caused as a consequence of a distorted and misled public perception. Useful chemicals can be lost by attrition even without regulatory intervention, because of unfounded changes in public behavior and precautionary reaction of industry. In many cases, the categorization of a chemical by hazard-identification alone diverts effort and funding into research projects which continue long after the chemical has been determined not to pose a risk to humans or effective risk management actions have been taken. For instance, the NCI bioassay on chloroform was published in 1976 (NCI, 1976) but over 90 papers have been published concerning its carcinogenicity (PubMed, 2016). As recently as 2010, Take et al. (2010) investigated interactions in kinetics of chloroform via the oral and inhalation routes in an attempt to put the results of the original high dose oral dosing based bioassay into the context of human exposure which is mainly by inhalation or via the dermal route (Take et al., 2010).

11. Problem formulation: what problem is being addressed?

"The mere formulation of a problem is far more essential than its solution, which may be merely a matter of mathematical or experimental skill. To raise new questions, new possibilities, to regard old problems from a new angle require creative imagination and marks real advances in science." – Albert Einstein (1938).

Formulating the problem being addressed is key to solving it. Which problems are the hazard-identification based classification systems trying to address?

In the 1970s the problem could have been formulated as "identify those chemicals which are capable of causing cancer so they can be eliminated from use". The processes put into place based on this problem formulation were set up in favor of

Please cite this article in press as: Boobis, A.R., et al., Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society, Regulatory Toxicology and Pharmacology (2016), http://dx.doi.org/10.1016/j.yrtph.2016.10.014

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identifying carcinogens, i.e. set up to minimize false negatives. The problem was formulated with the assumption that there would be a relatively small number of carcinogens which could be detected with reasonable reliability and did not foresee that there would turn out to be various mechanisms of carcinogenicity with different implications for risk assessment and risk management, and that a number of these would be specific to rodents. Most of the chemicals identified up to that time were potent DNA-reactive (genotoxic) carcinogens that produced cancer in both rodent models and in humans, such as aromatic amines, polycyclic aromatic hydrocarbons, nitrosamines and aflatoxins. These were believed to not have a threshold. With the development of the two year rodent bioassay incorporating an MTD, numerous chemicals were identified as carcinogenic that were non-DNA reactive (non-genotoxic). Their cancer modes of action considered to be secondary consequence of their toxicity (e.g. sustained cytotoxicity or cell proliferation) and were considered to have a threshold. Subsequent research has shown that many produce cancer in rodents by a mode of action not relevant to humans. If relevant to humans, the presence of a threshold presents a completely different dose response and risk assessment than the DNA reactive carcinogens. Hazard-based systems do not distinguish these, even though potency and human risk are vastly different.

Hazard-identification based classification systems could have a part to play in addressing an updated problem formulation as an early warning or priority setting measure. There could be value if the processes used were rapid and were undertaken before more detailed risk assessment is completed and if they were acknowledged to provide a preliminary evaluation which would subsequently be refined as necessary. However, the current hazard-identification based systems are not treated as preliminary assessments leading to the problems which have been described in section 10.

Systems which are designed to place as many chemicals as possible into the most severe category are ultimately self-defeating. At first sight this could appear to be a benefit. More chemicals will be classified in the most severe category and would be subjected to stringent risk management, which in a hazard-identification only system means no exposure. This could be achieved at a fraction of the cost simply by assuming that all chemicals are carcinogens. But placing more and more chemicals into the most extreme category will have a severe unintended effect. In fact, when only the most hazardous chemicals are identified, the classification is respected and appropriate risk management decisions are taken, especially in those sectors where banning or withdrawal is not mandatory. However, if too many chemicals are placed into the most hazardous category, including those which do not represent an extreme risk, the distinction is lost, and respect for the system is eroded (American Cancer Society, 2016).

Many sectors will find it hard to operate by excluding all chemicals in this category and chemicals truly hazardous by adverse effects other than carcinogenicity may not be excluded or managed appropriately, thereby having the opposite effect from the intended one. For example, many chemicals that are natural components of various foods produce cancer in rodents at high doses, including substances in fruits and vegetables, which most people consider positive enhancers to health (Ames and Gold, 1990). Likewise, more than half of currently approved prescription pharmaceuticals are carcinogenic in rodent bioassay, and yet, based on a risk assessment rather than a hazard-based analysis, they benefit millions of grateful patients, with little or no risk of cancer (Brambilla et al., 2012).

It is now time to revise the problem formulation statement along the lines of "identify and characterize the carcinogenic potential of chemicals so that appropriate risk management measures can be taken to safeguard human health."

This is the direction being taken by several national and international initiatives (e.g., Health Canada, 2000; WHO IPCS, 2010; EFSA, 2013). The US EPA Framework for Human Health Risk Assessment to Inform Decision Making (EPA, 2014) outlines a stepwise approach that goes through Planning and scoping; Problem formulation; Risk assessment; Exposure and effects assessment (including hazard-identification and dose response assessment); Risk characterization; Public, stakeholder and community involvement; Informing decisions. The RISK21 process (Embry et al., 2014) emphasizes the importance of problem formulation, the use of existing data, and tiered assessment of exposure and then hazard in safety assessment.

Much has been achieved by international co-operation in advancing risk assessment it is now time for the categorization of carcinogenicity to be the subject of such an initiative. The WHO International Programme for Chemical Safety last reviewed classification schemes in 1995 (IPCS, 1995) and recognized the need to consider a range of issues which would need resolution to solve the problem of diverging classification schemes. These issues have been clarified in the intervening 20 years, and it is now the time to heed the call in the Lancet (Lancet, 2016) for an international initiative to develop a standardized, internationally agreed upon methodology for carcinogen assessment, coupled with tools for presenting results that are easily understood and accepted by all interested parties.

12. Reproductive toxicology and endocrine disruption

This paper has focused on cancer but there are other areas of toxicology in which hazard-identification based classification systems exist, with similar untoward consequences. The classification system for reproductive and developmental toxicity in the EU is also a hazard-identification based system (Hennes et al., 2014). Classification as a Category 1A (known human reprotoxicant) or 1B (presumed human reprotoxicant) will trigger downstream automatic extreme risk management measures for some uses of chemicals, for instance plant protection products (EU, 2009) using the so-called "cut-off" criteria. This causes similar problems to those caused by the hazard-identification based system for carcinogenicity within the EU. For example, vitamin A at high doses is a known human teratogen (Rothman et al., 1995). In a hazard-based classification system it should be banned, and yet lower exposures are essential for life. These problems are being reviewed in a Consultation on the Regulatory Fitness of Chemicals Legislation (EU, 2016a,b).

Recently the EU published the proposed criteria for identifying chemicals which have the potential to cause adverse effects via endocrine disruption, but the proposed classification does not include an assessment of potency (EU, 2016a). It does not seem to be sensible to introduce a new hazard-identification based system with all the problems that entails at the same time as the EU is reviewing the impact of such systems (EU, 2016b).

13. Conclusions

Hazard-identification based classification schemes are inadequate to guide appropriate risk management decisions and have become outmoded. They are based on a concept developed in the 1970s that chemicals could be categorically divided cleanly into two classes: carcinogens and non-carcinogens. It was postulated at that time that a major reduction in cancer incidence would result if carcinogens could be identified and then eliminated from use and from the environment (Rettig, 2007). The classification that these schemes provide is based on the strength of evidence that the

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chemical has some degree of carcinogenic potential in humans or rodents but they do not indicate the degree of risk following real human exposure.

Categorization by the strength of evidence that a chemical has caused cancer in humans or in laboratory animals can place chemicals and agents with widely differing potencies in their ability to cause cancer and with very different modes of action into the same category. Chemicals with seven orders of magnitude difference in the dose required to cause cancer can be placed in the same category. This is how eating processed meat can fall into the same category as sulfur mustard gas.

More modern strategies based on problem formulation and hypothesis-based approaches in a risk decision framework such as those described by the US EPA (EPA, 2005; EPA, 2014), the UK Committee on Carcinogenicity (CoC, 2012), the EU Scientific Committee on Occupational Exposure Limits (Bolt and Huici-Montagud, 2008) provide clearer guidance and allow informed risk management decisions to be taken. Once carcinogenic potential has been identified, hazard characterization then examines other factors such as the dose response and the mode of action to be combined with exposure assessment leading to risk assessment. Only then can risk management actions be taken if appropriate.

The hazard and risk characterization approach avoids the unintended downsides of creating health scares, incurring unnecessary economic costs and the diversion of public funds, which could be spent more wisely, into unnecessary research.

An international initiative to agree upon a standardized, internationally acceptable methodology for carcinogen assessment is needed now. The approach taken should incorporate principles and concepts of existing international consensus-based frameworks including the WHO IPCS mode of action framework.

Declaration of interests

This work did not receive any specific support from funding agencies in the public, commercial, or not-for-profit sectors.

The authors' affiliations are as shown on the cover page. The authors had sole responsibility for the writing and content of the paper. The views and opinions expressed in the paper are those of the authors, and do not necessarily reflect the views or policies of the authors' current or former employers.

The authors have served as members of the following panels or committees and/or for the following organisations:

Council of Canadian Academies (VD); European Food Safety Authority (AB, AM); European Centre for Ecotoxicology and Toxicology of Chemicals (AB, JD); EU Scientific Committee on Occupational Exposure Limit Values (AM); European Medicines Agency (AB); Health Canada (PF-C); International Agency for Research on Cancer (SC, DW); International Life Science Institute (AB, SC, JD, VD, PF-C, AM, JS, RS, DW); Joint WHO/FAO Meeting on Pesticides Residues (AB, VD, PF-C); Italian Committee on Pesticides (AM); Joint WHO/FAO Expert Committee on Food Additives (Residues of Veterinary Drugs) (AB); National Institutes of Health (SC); National Academy of Sciences (SC, PF-C, RS); National Institute of Environmental Health Sciences (SC, DW); National Toxicology Program (SC, VD, PF-C, JS, DW); Organization for Economic Cooperation and Development (VD, PF-C, JS, RS); Swiss Centre for Applied Human Toxicology (AB, AM); UK Advisory Committee on Pesticides (AB); United Kingdom Committee on Carcinogenicity (AB, JD); UK Committee on the Medical Effects of Air Pollutants (AB); UK Committee on Residues of Veterinary Drugs (AB); UK Committee on Toxicity (AB); United States Environmental Protection Agency (SC, VD, PF-C, JS, RS, DW); United States Food and Drug Administration (SC, PF-C); World Health Organization International Program on Chemical Safety (AB, SC, JD, VD, PF-C, AM, JS, RS).

VD is retired from the US Environmental Protection Agency.

PF-C is retired from the US Environmental Protection Agency and the International Life Sciences Institute.

JS is retired from the US Environmental Protection Agency.

RS is retired from the US Environmental Protection Agency.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.yrtph.2016.10.014.

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