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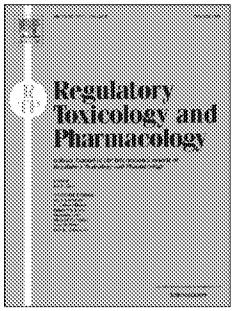

Classification schemes for carcinogenicity based on hazard-identification have become outmoded and serve neither science nor society

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1 **Classification Schemes for Carcinogenicity Based on Hazard-identification Have Become Outmoded**

2 **and Serve neither Science nor Society**

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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.

Highlights

- Cancer classification schemes based on hazard-identification such IARC and UN GHS are outmoded and inadequate to manage chemical risks
- Chemicals with many orders of magnitude difference in potency and modes of action are placed in the same category
- Unintended consequences of unnecessary health scares, economic costs, loss of beneficial products, and diversion of public funds

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- Globally accepted problem formulation and hypothesis-based frameworks provide modern approaches based on hazard and risk characterization
- Call for an international initiative to develop a consensus on classification methodology for carcinogenicity assessment

Key Words: Classification; Hazard Characterization; Risk Assessment; Carcinogenicity; IARC; GHS

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69 Abbreviations

70 ACGIH – American Conference of Government Industrial Hygienists

71 CoC – United Kingdom Committee on Carcinogenicity

72 ECHA - European Chemicals Agency

73 EFSA – European Food Safety Authority

74 EPA – United States Environmental Protection Agency

75 EU – European Union

76 GHS - United Nations Global Harmonized System for Classification and Labelling

77 IARC – International Agency for Research on Cancer

78 IPCS – International Programme on Chemical Safety

79 JMPR –Joint FAO/WHO Meeting on Pesticide Residues

80 MOA – Mode of Action

81 NCI – United States National Cancer Institute

82 PMRA - Health Canada Pest Management Regulatory Agency

83 WHO – World Health Organization

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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 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

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110 to confusion; should we treat processed meat as we do sulfur mustard gas – reduce exposure to
111 zero; or should we treat sulfur mustard gas as we do red meat – consider it part of a healthy life style
112 in moderation? This categorization can thus lead to unnecessary public anxiety; resources may be
113 diverted that would be better used addressing more substantial problems; safe and useful products
114 come under unnecessary and excessive scrutiny; and they may even be replaced by other less
115 characterized and potentially less safe products.
116
117 This present work describes the origins of classification schemes based on hazard-identification,
118 acknowledges that they were once useful, explains why they no longer serve a useful role and
119 illustrates how science-based approaches in a risk based decision framework are more suited to
120 protecting human health in the 21st century.
121

122 **2. Advances in Public Health and Chemical Risk Management**

123 The 20th century saw great advances in the state of public health; managing the potential risks from
124 chemicals has played its part. Life expectancy increased by over 30 years in Europe and the Americas
125 between 1900 and 2000 (Roser, 2015). Certain chemicals and technologies developed in the late
126 19th century and early 20th century did come at a price, however. At the time, there was poor
127 understanding of the range of biological effects that chemicals could cause until the pioneering
128 observational studies that identified how chemicals could adversely affect human health were
129 published (Goldblatt, 1944). Many adverse effects observed in humans were then verified in animal
130 studies. By the middle of the 20th century there was a shift towards the use of animal studies to
131 predict what could happen in humans, which led, in the 60's and 70's, to the development of
132 extensive and diverse toxicological studies to identify and characterize chemical hazards, and predict
133 the human safe dose, before adverse effects could occur in humans. Hazard-identification and
134 characterization via animal studies became the standard for predicting and then avoiding potential

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135 adverse effects in humans. As a result of this approach to chemical safety assessment, exposure to
136 high-risk chemicals has been progressively reduced (Kauppinen et al, 2013). Whilst not perfect, this
137 approach has the advantage that chemicals potentially toxic to humans are identified before there is
138 any human exposure.
139

140 **3. Classification and Risk Assessment**

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

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

156

157 Classification uses a different approach while being based on similar principles. It focuses on the
158 hazard which has been identified, usually from animal studies and, then, grades the hazard into

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159 various categories based on the severity and, in some instances, dose response. Classification was
160 originally intended to provide information on the effects of a chemical following acute exposure for
161 labelling purposes for transport (UN, 2011). However, its use has broadened substantially so that
162 many regulatory schemes are based solely on classification for a range of end points following either
163 acute or repeated exposure leading directly to risk management action without consideration of the
164 chemical potency, severity of the effect or mode of action or the nature and extent of human
165 exposure.

166

167 **4. Problems with Classification**

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

180

181 These problems arise most often when the classification process focuses simply on identifying the
182 hazard but does not go on to characterize the hazard in terms of severity, dose response and mode

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183 of action. This is the situation with some schemes in the areas of carcinogenicity, and reproductive
184 toxicity, and it is a source of the current controversy on how to prioritise and manage the risk posed
185 by chemicals identified as endocrine disrupters. The omission of characterization of both hazard
186 and risk in these schemes stems from the historical special treatment given to certain health effects
187 based on their public perception (Slovic, 1987) such as carcinogenic and reproductive toxicity effects,
188 and more recently endocrine disruption, neurotoxicity and immunotoxicity.

189

190 **5. Cancer as a Major Concern**

191 Cancer had become such a concern that in 1971 US President Nixon signed the National Cancer Act
192 saying in his State of the Union Address "The time has come when the same type of concentrated
193 effort that split the atom and took a man to the moon should be turned toward conquering this
194 dread disease". Large sums of money were devoted to reducing cancer deaths and prevention was
195 seen as part of the "war on cancer" as well as the discovery and development of treatments. It was
196 believed, at the time, that a large proportion of cancers were caused by industrial chemicals. Hueper
197 (1955) from the National Cancer Institute (NCI) had concluded that cancer from exposure to
198 industrial chemicals was of far greater concern than cancer from tobacco smoking. This has since
199 been shown to be incorrect as tobacco smoking is now recognized as the second leading cause of
200 death globally, with 6.3 million deaths annually attributed to smoking (GBD2010).

201 In the middle of the 20th century, the concept developed that chemicals could be segregated into
202 two classes: carcinogens and non-carcinogens. It was postulated that a major reduction in cancer
203 incidence would result if we could identify the "carcinogens" and, hence, replace them with "non-
204 carcinogens". This concept started the drive towards using hazard-identification alone for
205 carcinogenicity which has continued for nearly half a century in a largely unmodified way. It was also
206 the basis for the use of the Maximum Tolerated Dose in animal studies which was thought to
207 optimize the chances of identifying "carcinogens". Whilst the concept was considered sound in

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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

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232 health protection, the carcinogenicity scheme deliberately avoided the valuable context of hazard or
233 of dose response, severity, and mode of action or exposure. At the time this scheme was put in
234 place, such characterization was not thought necessary as the aim was simply to identify
235 "carcinogens" and to eliminate them.

236

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

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

253 Thus a system set up half a century ago based on an overly simplistic concept as an initial attempt to
254 address the disease burden of cancer has found its way into classification schemes for chemicals and
255 also into some downstream risk management processes. The consequences may not have been

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256 intended but they were predictable. The pressure to replace a chemical which had been identified as
257 a potential human carcinogen was immense, even on the basis of animal studies, and the very act of
258 categorizing a chemical in this way leads to a stigma which would often result in major changes in its
259 use, including withdrawal, whereas risk-based assessments show that there is reasonable certainty
260 no harm will result from its use.

261

262 **7. Introduction of the Cancer Bioassay**

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

274

275 The bioassay was intended for hazard-identification and was therefore designed to maximize the
276 ability to detect "carcinogenicity". Dosing was for as much of the life time of the animals as possible.
277 Historically, exposure started after weaning, some newer study designs start exposure before birth.
278 The highest dose was set as a Minimally Toxic Dose that would not impact the animals' normal
279 lifespan from effects other than cancer. This evolved into the Maximum Tolerated Dose (MTD),

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280 which increased the doses used in an attempt to increase sensitivity to detect the "carcinogenicity"
281 of low potency compounds. Under these assay conditions 50% of chemicals, both synthetic and
282 natural, were capable of increasing the incidence of neoplasms (both malignant and benign) (Gold et
283 al 1989). Numerous studies have shown that as the experimental dose of a chemical is increased,
284 different saturable or inducible toxicokinetic (e.g., metabolism, uptake, excretion) and
285 toxicodynamic (e.g., homeostasis, receptor interactions, protein binding, repair mechanisms)
286 processes involved in chemical toxicity (e.g., tumorigenicity) can be involved, which may not be
287 engaged at environmental exposures (Slikker et al 2004a,b). It seems that the high doses used were
288 triggering different mechanisms which lead to the development of neoplasms in laboratory animals.
289 Determining which mechanisms are operative along the dose-response curve has important
290 implications for interpreting bioassay data for the purposes of predicting human risk.

291

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

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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 harmonised 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-Mullen 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

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329 had been done and to emphasize that MoA analyzes should be problem formulation-based
330 recognizing that MOA knowledge can inform different risk management decisions: priority setting,
331 read across, or guiding research, not just for risk assessment where it has been most frequently used
332 (Meek et al.2014).
333
334 When using this approach for assessing carcinogenicity, there are three broad outcomes which have
335 an impact on how the chemical should be further evaluated:

336 ∞ Rodent carcinogens that are considered relevant for humans and which have mode(s) of
337 action indicating that there is no presumption of a threshold for the dose response.
338 ∞ Rodent carcinogens that are considered relevant for humans and which have a mode(s) of
339 action indicating that there is a threshold for the dose response. These often result from
340 modes of action associated with the high experimental treatment doses that result in
341 secondary processes (e.g., sustained cytotoxicity and compensatory hyperplasia) where a no
342 effect level or margin of safety can be established. A substantial number of chemicals have
343 been shown to fall into this group including the pesticides acifluorfen sodium, amitrole,
344 captan, cyproconazole, folpet, lactofen, and pyroxasulfone (EPA, 2015)
345 ∞ Rodent carcinogens that are considered to have mode(s) of action not relevant for humans.
346 A number of chemicals induce tumors by modes of action well documented to be non-
347 relevant to humans. Some examples are: kidney tumors in male rats associated with
348 substances causing α2u-globulin nephropathy ;pheochromocytomas in male rats exposed to
349 particulates through inhalation secondary to hypoxemia; Leydig cell adenomas induced by
350 dopamine antagonists or gonadotropin-releasing hormone (GnRH); certain thyroid tumors in
351 rodents mediated by UDP glucuronyltransferase (UGT) induction (listed in the Classification
352 Guidelines by ECHA, 2013).
353

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354 The process for the assessment of the carcinogenicity of chemicals by many regulatory authorities or
355 organisations has incorporated the concept that different modes of action have different
356 implications for human safety. Examples are:
357
358 *US EPA* - The US EPA (2005) revised their Cancer Risk Assessment Guidelines to bring in more
359 relevant science in the cancer risk assessment process by incorporating a framework for analyzing
360 mode of action (consistent with the WHO IPCS approach). The US EPA also replaced their cancer
361 categories with descriptors and weight of evidence narratives, and to acknowledge that carcinogens
362 should be considered in ways appropriate to their full hazard and risk characterization. In the
363 absence of data, the US EPA takes a public health protective position that animal tumor findings are
364 assumed to be relevant to humans, and cancer risks are assumed to conform with the default
365 hypothesis of non-threshold, low dose linearity. However, sufficient, scientifically justifiable mode of
366 action information can support different conclusions. Non-linear dose response modelling may be
367 appropriate. In some cases, the animal tumors are concluded to be not relevant to humans and thus
368 not to be used in human risk assessment. These considerations are reflected in the descriptors
369 which the EPA applies. More than one descriptor can be used when an agent's effects differ by dose
370 or exposure route. For example, an agent may be "Carcinogenic to Humans" by one exposure route
371 but "Not Likely to Be Carcinogenic" by a route by which it is not absorbed. Also, an agent could be
372 "Likely to Be Carcinogenic" above a specified dose but "Not Likely to Be Carcinogenic" below that
373 dose because a key event in tumor formation does not occur below that dose. These are descriptors
374 which enable the US EPA to apply the appropriate risk assessment methodology.
375
376 *ACGIH* - The American Conference of Government Industrial Hygienists (ACGIH, 2016) has developed
377 categories which describe different classifications based on the concept that different modes of
378 action have different implications for human safety:
379 • A1- Confirmed human carcinogen

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380 • A2 - Suspected human carcinogen

381 • A3 - Animal carcinogen. The agent is not likely to cause cancer in humans except under
382 uncommon or unlikely routes or levels of exposure. The agent is carcinogenic in
383 experimental animals at a relatively high dose, by route(s) of administration, at site(s), of
384 histologic type(s), or by mechanism(s) that may not be relevant to worker exposure.

385 • A4 - Not classifiable as a human carcinogen

386 • A5 - Not suspected as a human carcinogen

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

391 ∞ Exposure should be as low as reasonably possible for substances with a genotoxic mode of
392 action

393 ∞ Exposure should be below a level set using identification of critical end points and use of
394 uncertainty factors for substances with other modes of action considered relevant to
395 humans.

396 ∞ Exposure should be below levels determined by consideration of non-carcinogenicity end-
397 points for substances with modes of action for carcinogenicity considered non-relevant to
398 humans.

399

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

403 A) Non-threshold genotoxic carcinogens; for low-dose assessment of risk, the linear non-
404 threshold (LNT) model appears appropriate. For these chemicals, regulations (risk

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

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

418

419 9. **Unchanged Processes Become Outmoded**

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

425

426 The EU Classification and Labelling Guidelines (ECHA 2012) uses a system based on the strength of
427 evidence for hazard-identification as a "carcinogen". The guidelines allow for a chemical to be
428 classified as not a carcinogen if a mode of action can be established to be not relevant to humans.

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429 However, for carcinogens that are considered relevant for humans, the system does not distinguish
430 between those which have a mode of action indicating that there is a presumption of no threshold
431 for the dose response and those which have a mode of action indicating that there is a threshold for
432 the dose response.
433

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

442

443 **10. Problems Resulting From Use of Outmoded Processes**

444 The problems caused by hazard-identification classification schemes are complex and they have
445 consequences for many parts of society. The original intent of these schemes was to identify
446 chemicals or other agents which may be of concern and thus require further evaluation including full
447 risk assessments to determine if action would be needed to mitigate a risk. We see this process
448 working in the strategy used by the EPA (EPA, 2005) and UK Committee on Carcinogenicity (CoC,
449 2012) where the initial hazard-identification as a carcinogen triggers a logical and scientific
450 consideration of the risk to human health which takes into account the potency, the mode of action
451 and the magnitude, duration, frequency and route of exposure. Appropriate risk mismanagement
452 decisions can then be made which can range from taking no action, using personal protective

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453 equipment, decreasing personal exposure, restrictions on use, to outright banning of use in extreme
454 circumstances.

455 However, all too often the public response to the classification by hazard-identification alone is not
456 so reasoned. For example IARC classification as "carcinogenic to humans", "probably carcinogenic to
457 humans" or "possibly carcinogenic to humans" can all lead to negative publicity and a "health scare".
458 The "health scare" can trigger anxiety and lead to behavior which is detrimental to actually achieving
459 desirable public health goals (Berry, 2016). Government and other agencies then have to use
460 precious resources to respond because of publicly perceived rather than actual threats.
461

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

473

474 Cancer UK (2012) explains that *"IARC categories are designed to flag things up to policy makers, so*
475 *they can then analyse the scale of the problem, weigh the risks against the benefits, and bring in*
476 *appropriate legislation."* IARC sometimes assesses chemicals after they have already been
477 considered in detail for both potential hazard and risk by stringent agencies responsible for

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478 regulation, such as US EPA, EFSA, ECHA, JMPR, PMRA. This lack of coordination and co-operation
479 can lead to problems, confusion, duplication of efforts, and the expenditure of unnecessary
480 resources. A recent example of this has arisen with the herbicide glyphosate. The European Food
481 Safety Authority has completed an extensive review of its original evaluation following a second
482 mandate from the European Commission (EFSA, 2015) to consider the findings from IARC's
483 classification of glyphosate as *"a probable human carcinogen"* (IARC, 2015), They came to the
484 conclusion that *"glyphosate is unlikely to pose a carcinogenic hazard to humans and the evidence*
485 *does not support classification with regard to its carcinogenic potential" (EFSA 2015).* Oddly, IARC
486 reviewers have chosen to dispute the findings of the EFSA process and criticize EFSA for "*an over-*
487 *reliance on non-publicly available industry-provided studies using a limited set of assays that define*
488 *the minimum data necessary for the marketing of a pesticide*" (Portier et al 2016). In the case of
489 pesticides, it is the legal responsibility of the regulated industry to provide all the studies needed to
490 establish the safety of their products. Extensive data are legally mandated by regulatory authorities
491 to enable them to evaluate efficacy and safety, and these data are generated in accordance with
492 Good Laboratory Practice and a series of internationally harmonized and scientifically peer-reviewed
493 study protocols, designed to maintain a high standard of scientific quality and consistency, and to
494 provide confidence that study results are repeatable and acceptable. So it should not be surprising
495 that there are large databases of studies sponsored by pesticides registrants given the legal and
496 regulatory requirements by authorities, who have access to all the raw data. It is noteworthy that
497 based on an weight of evidence approach that evaluates the consistency, dose response, time
498 course, and biological plausibility of all relevant evidence, JMPR concluded that glyphosate *"is*
499 *unlikely to pose a carcinogenic risk to humans from exposure through the diet*" (JMPR, 2016). EPA
500 recently articulated its conclusions that "*The strongest support is for "not likely to be carcinogenic to*
501 *humans at doses relevant to human health risk assessment.""* (EPA 2016)
502

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

513

514 Chemicals and other agents, particularly those that are in widespread use that are flagged by
515 classification processes based on hazard-identification alone tend to come under close scrutiny and
516 become the subject of debate and concerted public campaigns. For instance the IARC classification
517 of glyphosate has given rise to headlines such as "War in Europe- Battle over Glyphosate" (Genetic
518 Literacy Project, 2016), "EU scientists in row over safety of Glyphosate weedkiller" Guardian (2016),
519 and "How the World Health Organization's cancer agency confuses consumers" (Reuters, 2016). The
520 listing of a chemical by these hazard-identification only based schemes can have major implications
521 either because of downstream regulation or because of the reputational damage which can be
522 caused as a consequence of a distorted and misled public perception. Useful chemicals can be lost
523 by attrition even without regulatory intervention, because of unfounded changes in public behavior
524 and precautionary reaction of industry. In many cases, the categorization of a chemical by hazard-
525 identification alone diverts effort and funding into research projects which continue long after the
526 chemical has been determined not to pose a risk to humans or effective risk management actions
527 have been taken. For instance, the NCI bioassay on chloroform was published in 1976 (NCI, 1976)

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528 but over 90 papers have been published concerning its carcinogenicity (PubMed 2016). As recently
529 as 2010, Take et al (2010) investigated interactions in kinetics of chloroform via the oral and
530 inhalation routes in an attempt to put the results of the original high dose oral dosing based bioassay
531 into the context of human exposure which is mainly by inhalation or via the dermal route (Take et al,
532 2010).
533

534 **11. Problem Formulation: What Problem is Being Addressed?**

535 "The mere formulation of a problem is far more essential than its solution, which may be merely a
536 matter of mathematical or experimental skill. To raise new questions, new possibilities, to regard old
537 problems from a new angle require creative imagination and marks real advances in science." –
538 Albert Einstein (1938).
539

540 Formulating the problem being addressed is key to solving it. Which problems are the hazard-
541 identification based classification systems trying to address?
542

543 In the 1970s the problem could have been formulated as "identify those chemicals which are
544 capable of causing cancer so they can be eliminated from use". The processes put into place based
545 on this problem formulation were set up in favor of identifying carcinogens, i.e. set up to minimize
546 false negatives. The problem was formulated with the assumption that there would be a relatively
547 small number of carcinogens which could be detected with reasonable reliability and did not foresee
548 that there would turn out to be various mechanisms of carcinogenicity with different implications for
549 risk assessment and risk management, and that a number of these would be specific to rodents.
550 Most of the chemicals identified up to that time were potent DNA-reactive (genotoxic) carcinogens
551 that produced cancer in both rodent models and in humans, such as aromatic amines, polycyclic
552 aromatic hydrocarbons, nitrosamines and aflatoxins. These were believed to not have a threshold.
553 With the development of the two year rodent bioassay incorporating an MTD, numerous chemicals

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554 were identified as carcinogenic that were non-DNA reactive (non-genotoxic). Their cancer modes of
555 action considered to be secondary consequence of their toxicity (e.g. sustained cytotoxicity or cell
556 proliferation) and were considered to have a threshold. Subsequent research has shown that many
557 produce cancer in rodents by a mode of action not relevant to humans. If relevant to humans, the
558 presence of a threshold presents a completely different dose response and risk assessment than the
559 DNA reactive carcinogens. Hazard-based systems do not distinguish these, even though potency and
560 human risk are vastly different.
561
562 Hazard-identification based classification systems could have a part to play in addressing an updated
563 problem formulation as an early warning or priority setting measure. There could be value if the
564 processes used were rapid and were undertaken before more detailed risk assessment is completed
565 and if they were acknowledged to provide a preliminary evaluation which would subsequently be
566 refined as necessary. However, the current hazard-identification based systems are not treated as
567 preliminary assessments leading to the problems which have been described in section 10.
568
569 Systems which are designed to place as many chemicals as possible into the most severe category
570 are ultimately self-defeating. At first sight this could appear to be a benefit. More chemicals will be
571 classified in the most severe category and would be subjected to stringent risk management, which
572 in a hazard-identification only system means no exposure. This could be achieved at a fraction of the
573 cost simply by assuming that all chemicals are carcinogens. But placing more and more chemicals
574 into the most extreme category will have a severe unintended effect. In fact, when only the most
575 hazardous chemicals are identified, the classification is respected and appropriate risk management
576 decisions are taken, especially in those sectors where banning or withdrawal is not mandatory.
577 However, if too many chemicals are placed into the most hazardous category, including those which
578 do not represent an extreme risk, the distinction is lost, and respect for the system is eroded
579 (American Cancer Society, 2016).

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580

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

590

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

594

595 This is the direction being taken by several national and international initiatives (e.g., Health
596 Canada 2000; WHO IPCS 2010; EFSA 2013). The US EPA Framework for Human Health Risk
597 Assessment to Inform Decision Making (EPA, 2014) outlines a stepwise approach that goes through
598 Planning and scoping; Problem formulation; Risk assessment; Exposure and effects assessment
599 (including hazard-identification and dose response assessment); Risk characterization; Public,
600 stakeholder and community involvement; Informing decisions. The RISK21 process (Embry et al,
601 2014) emphasizes the importance of problem formulation, the use of existing data, and tiered
602 assessment of exposure and then hazard in safety assessment.

603

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604 Much has been achieved by international co-operation in advancing risk assessment it is now time
605 for the categorization of carcinogenicity to be the subject of such an initiative. The WHO
606 International Programme for Chemical Safety last reviewed classification schemes in 1995 (IPCS,
607 1995) and recognized the need to consider a range of issues which would need resolution to solve
608 the problem of diverging classification schemes. These issues have been clarified in the intervening
609 20 years, and it is now the time to heed the call in the Lancet (Lancet, 2016) for an international
610 initiative to develop a standardized, internationally agreed upon methodology for carcinogen
611 assessment, coupled with tools for presenting results that are easily understood and accepted by all
612 interested parties.
613

614 **12. Reproductive Toxicology and Endocrine Disruption**

615 This paper has focused on cancer but there are other areas of toxicology in which hazard-
616 identification based classification systems exist, with similar untoward consequences. The
617 classification system for reproductive and developmental toxicity in the EU is also a hazard-
618 identification based system (Hennes et al, 2014). Classification as a Category 1A (known human
619 reprotoxicant) or 1B (presumed human reprotoxicant) will trigger downstream automatic extreme
620 risk management measures for some uses of chemicals, for instance plant protection products (EU
621 2009) using the so-called "cut-off" criteria. This causes similar problems to those caused by the
622 hazard-identification based system for carcinogenicity within the EU. For example, vitamin A at high
623 doses is a known human teratogen (Rothman et al, 1995). In a hazard-based classification system it
624 should be banned, and yet lower exposures are essential for life. These problems are being reviewed
625 in a Consultation on the Regulatory Fitness of Chemicals Legislation (EU, 2016).
626

627 Recently the EU published the proposed criteria for identifying chemicals which have the potential to
628 cause adverse effects via endocrine disruption, but the proposed classification does not include an
629 assessment of potency (EU 2016, a). It does not seem to be sensible to introduce a new hazard-

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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, 2005). The classification that these schemes provide is based on the strength of evidence that the 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

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653 management decisions to be taken. Once carcinogenic potential has been identified, hazard
654 characterization then examines other factors such as the dose response and the mode of action to
655 be combined with exposure assessment leading to risk assessment. Only then can risk management
656 actions be taken if appropriate.
657
658 The hazard and risk characterization approach avoids the unintended downsides of creating health
659 scares, incurring unnecessary economic costs and the diversion of public funds, which could be spent
660 more wisely, into unnecessary research.
661

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

666

667 **Declaration of Interests**

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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.

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