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Review

Banding carcinogenic risks in developed countries: A procedural basis for qualitative assessment

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Abstract

Readily achieved comparative assessment of carcinogenic risks consequent upon environmental exposures may increase understanding and contribute to cancer prevention. Procedures for hazard identification and quantitative risk assessment are established, but limited when addressing novel exposures to previously known carcinogens or any exposure to agents having only suspected carcinogenic activity. To complement other means of data evaluation, a procedure for qualitative assessment of carcinogenic risk is described. This involves categorizing the relevant carcinogen and circumstances under which exposure occurs. The categories for carcinogens are those used for hazard identification and involve whether the agent is (1) a recognized carcinogen for humans; (2) probably or (3) possibly carcinogenic for humans; (4) characterized by inadequate evidence of carcinogenicity; or (5) lacking carcinogenicity. Exposure is categorized by whether it is one which (1) establishes the agent as a recognized carcinogen; (2) is taken into account in establishing carcinogenicity status; (3) is distinct from those providing clearest evidence of carcinogenicity; (4) is not characterized in relation to carcinogenicity; or (5) involves an exposure in which absence of carcinogenic outcome is observed. These two categories of evidence allow the risk inherent in a situation to be banded as indicative of a *proven, likely, inferred, unknown* or *unlikely carcinogenic outcome*, and further characterized using sub-bands. The procedure has been applied to about fifty situations. For recognized carcinogens, including asbestos and polycyclic aromatic hydrocarbons, risks consequent upon occupational exposure, the impact of point source pollution, residence near contaminated sites and general environmental exposure are allocated across the *proven* band and a *likely* sub-band. For solvents, pesticides and other compounds having less clearly established carcinogenicity, impact on residents living near a production site, or near earlier related industrial activity is allocated to certain *inferred* sub-bands. *Unknown carcinogenic outcome*, which identifies exposure to an agent with inadequate evidence of carcinogenicity rather than being indicative of equivocal or negative data in any context, indicates both the impact of certain pollutants and user-exposure to some consumer products. Situations allocated to the *unlikely* risk band principally involve certain consumer products. Overall, such risk assessment may be of greatest worth in focusing community attention on proven causes of cancer and associated preventive measures.

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Keywords: Environmental carcinogens; Risk assessment; Occupational exposure; Environmental exposure; Pollution; Contamination; Consumer products; Cancer causation

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1. Introduction

Cancer is largely attributable to the impact of exogenous environmental factors, a wide spectrum of circumstances of exposure to particular carcinogens having been described [1]. In addition to situations well-recognized as contributing to increased risk of cancer, the general community is continually alerted by media references to people said to be at increased risk of cancer because of their exposure to particular carcinogenic agent(s). The concern that should be appropriately accorded to each such situation is rarely clear. Likelihood of cancer causation may be imputed because a putative carcinogen is newly described. More commonly, attention may be drawn to newly described circumstances of exposure to a recognized or previously suspected carcinogen. To address these and other situations presenting some degree of carcinogenic risk, a procedure for qualitative assessment has been developed and is outlined here. With reference to the impact of exogenous chemical or physical agents, it is thereby possible to indicate the likelihood of a carcinogenic outcome. The risk assessment procedure is based on criteria for categorizing, in qualitative terms, the evidence of carcino-

genicity for the agent involved, and for categorizing the circumstances of exposure to that agent. Such qualitative assessment of carcinogenic risk evolves from, and may be related to both hazard identification and quantitative risk assessment.

2. Data evaluation procedures for carcinogens

2.1. Hazard identification

For the purpose of primary prevention, hazard identification is a first step [2]. Hazard identification primarily involves evaluation of the epidemiological and experimental evidence that an agent is capable of causing an increased incidence of cancer in humans [3]. Apart from incidence, other parameters, including decreased latency period, may be considered. Information concerning mode and mechanism of action of the agent in question is increasingly taken into account in hazard identification [4,5]. The classification systems employed by some US and international authorities to rank carcinogenic hazards have been recently summarized [6]. Various terms have been adopted to indicate agents recognized

to be carcinogenic to humans, or probably, or possibly, or not assessable as, carcinogenic to humans. The outcomes of hazard identification are systematically presented in, for example, the *Report on Carcinogens* by the National Toxicology Program (NTP), an arm of US Department of Health and Human Services [7], and *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans*, produced by International Agency for Research on Cancer (IARC), an arm of World Health Organization [8]. Typically, the results of hazard identification are presented as lists of agents, categorized according to the degree of certainty with which each agent is known to cause cancer in humans. These lists belie a complex, and progressively evolving, evaluation process through which all relevant findings are addressed using a weight-of-evidence approach. Use of the term ‘qualitative risk assessment’ as a synonym for ‘hazard identification’ does not appear to be mandated by any authority and is misleading.

Hazard characterisation is an evaluation process based on criteria which are amongst those addressed in hazard identification and includes specific reference to existing toxicokinetic and/or toxicodynamic data to reach a conclusion about the likely shape of the dose–response curve for any carcinogenic effect [9]. A weight of evidence approach uses all available toxicological, metabolic and physio-chemical information about a compound for judging the likely potency of the compound in humans. Hazard characterisation may precede risk assessment.

Although having a critical place in cancer prevention, carcinogenic hazard identification has limitations. Firstly, hazard identification is usually undertaken only when adequate epidemiological or toxicological data are available. Secondly, the various lists of carcinogens are often long. They include many agents to which humans are exposed only in certain workplaces. Also in the context of hazard identification, it is proper to list agents because of carcinogenic effects observed fifty or more years ago, it being known that some such agents are no longer manufactured or used. Thirdly, hazard identification for a given agent is not qualified according to circumstances of exposure and, to that extent, is not fully informative. Thus, for example, the listing of ‘tobacco smoke’ as a recognized carcinogen does not differentiate between the circumstances of active smoking, environmental tobacco smoke and antenatal exposure as a consequence of parental smoking. Exposure to benzene may occur in the workplace, or as a consequence of atmospheric pollution by engine exhaust or because the solvent is present in bottled water. People exposed to cytotoxic drugs include cancer patients and also include some of those who care for them. Asbestos may be encountered by miners, or by those living in the vicinity of mines or by those drinking water from some sources. These various exposures may each warrant further consideration because, through hazard identification, a carcinogen is known to be involved. However, hazard identification does not provide for resources to be optimally apportioned according to the differing contexts in which exposure to a carcinogen may be known to occur.

2.2. Quantitative risk assessment

Carcinogenic hazard identification underpins quantitative risk assessment. Thus, for example, in 1983 the US National Research Council recognized that there are differences in the outcome of various modes of exposure to specific carcinogens, and the public health interventions that particular circumstances invite [10]. The key steps in quantitative risk assessment are hazard identification, exposure assessment, dose–response assessment and risk characterization [11].

Quantitative risk assessment is applied in determining the impact of chemicals in the workplace. Regulatory control of occupational exposure to carcinogens invariably requires extrapolation from the circumstances in which excess risk of cancer may have been described. The latter may have involved a relative risk as low as 1.20 (corresponding to an excess risk of 10^{-2}) which, to be determined in a retrospective cohort mortality study, would require approximately 4000 workers involved. Detecting at excess risk of 10^{-4} under the same circumstances may be calculated to require 40 million workers [12]. A risk of 10^{-5} or lower often underpins maximal levels of exposure specified by regulation [11].

In a broader environmental context, exposures leading to an excess risk of 10^{-5} or less are often the focus of quantitative risk assessments [13]. Thus Foran et al. [14], addressing dioxin-like compounds in salmon, determined upper-bound cancer risks as high as 1×10^{-3} when farmed fish are consumed more than twice per week. When salmon are consumed at frequencies that limit dioxin intake to 20% above background exposure, cancer risk declines to 2×10^{-4} , while consumption must be eliminated completely to achieve a risk (consequent upon other routes of exposure) of 1×10^{-5} which is within the range acceptable to the US Environmental Protection Agency. Thus for any such situation, there are multiple numeric findings [15]. Such complexity severely limits simple comparison between the quantitative risks evoked by different agents and differing exposures.

Quantitative risk assessment is subject to recognized uncertainties [16], specifically concerning the estimation of human cancer risk from exposure to environmental carcinogens at low doses [17]. Dose–response itself, as an indicator of potency and particularly if determined on the basis of quantified human exposure [18], provides a basis for comparing carcinogens. In animal bioassays, the amounts of chemical carcinogen required to induce tumours may vary by a factor of 10^8 depending upon species, route of administration and other parameters [19]. As an outcome of 2-year rodent studies, carcinogenic potency is defined as the lifetime relative risk per unit of average daily exposure [20]. Other experimental data available in the relatively short term may reduce dependency upon 2-year bioassay for this purpose [21,22]. The specification of potency may be used to compare carcinogens. However, as noted by Sanner et al. [23], determination of potency is not a substitution for quantitative risk assessment. Quantitation of carcinogenic risk (particularly that based on extrapolation over many orders of magnitude from animal studies without other relevant knowledge specifically including the mode of action of

the chemical) is most informative in a relative rather than an absolute sense (i.e., assessments indicate more or less risk when compared with each other, rather than being an accurate reflection of absolute risk).

Considered with reference to agents for which only some inference of carcinogenicity may be made, adequate dose–response and exposure data severely limit application of quantitative risk assessment. Thus, risk assessment in relation to pollutants such as pesticides, dioxins, and solvents may be inconclusive [24]. In short, although both hazard identification and quantitative risk assessment are established evaluation processes, these tools have recognized limitations. Qualitative risk assessment is also subject to limitations, but these limitations do not coincide with those just discussed. Qualitative risk assessment therefore provides a useful adjunct to hazard identification and quantitative risk assessment as a tool for expressing the outcome of environmental carcinogenesis in particular circumstances.

2.3. Qualitative risk assessment

Callahan and Sexton [25] comment that risk is not necessarily an intrinsically quantifiable variable. In principle, some form of qualitative risk assessment should precede quantitation of risk as a basis for considering whether the additional effort, inherent in making a quantitative assessment, should be invested. Qualitative assessment of carcinogenic risk is predicated on consideration of relevant carcinogenicity and exposure data [19,21,23]. Once evidence of carcinogenicity and evidence of exposure have been appraised, a qualitative assessment of the carcinogenic risk may be made. A key element in quantitative risk assessment, dose–response, is not taken into account as a separate parameter in qualitative risk assessment. Approaches to qualitative risk assessment include ALARA (as low as reasonably achievable) [9].

In a proposed procedure for qualitative risk assessment outlined in Section 3, evidence of exposure in relation to a particular situation is determined with reference to other circumstances in which humans are known to be exposed to the agent in question. This includes whether increased incidence of cancer has been causally (at one extreme) or inferentially (at the other) associated with that particular mode of exposure. Moreover, if epidemiological data concerning a specified situation are available, such findings are weighted ahead of data (including experimental studies involving the agent in question) which otherwise provide an inference of risk. As a result, the procedure described here is strongly influenced by epidemiological data. Using this procedure, specification of risk on the basis of experimental data alone may be made, but there is only limited power for discrimination. In relation to experimental data indicative of carcinogenicity, a different approach is required as exemplified by the IPCS Framework [26].

Considered in relation to some previous approaches to qualitative assessment of carcinogenic risk, a procedural basis for data evaluation is presented here. Through this procedure, risks are not determined according to the likelihood of a carcinogenic outcome arising from a given situation, which is

the province of quantitative risk assessment, but according to the nature of evidence indicating a carcinogenic outcome.

3. A procedural basis for qualitative risk assessment

3.1. Evidence of carcinogenicity

In deriving a procedural basis for qualitative risk assessment, it is immediately clear that evidence of carcinogenicity may be categorized in the manner presently used for hazard identification. Agents are categorized according to whether they are recognized to cause cancer in humans, probably cause cancer in humans, etc. [3]. The same criteria may be used in the context of qualitative risk assessment. Specifically, the criteria adopted here for categorizing evidence of carcinogenicity are those developed by IARC as summarized in Table 1, it being acknowledged that other criteria or terminology [6] could have been used. The prime consideration is that no new criteria need be considered specifically for this aspect of qualitative risk assessment. Making a qualitative risk assessment is not intended to involve an independent evaluation of epidemiological and/or experimental data as have been addressed in hazard identification. This will have involved such issues as the appropriateness and adequacy of meta-analyses and the weight accorded to negative studies, when relevant data are available.

To indicate that evidence of carcinogenicity is on the basis of hazard identification, the terms ‘probable carcinogen’ and ‘possible carcinogen’ are used (Table 1). The term ‘recognized carcinogen’ is adopted to specify a ‘Group 1 IARC’ (equivalent to ‘Part A NTP’) carcinogen; that is an agent established as causing cancer in humans. This usage of ‘recognized carcinogen’ allows the unqualified word ‘carcinogen’ to be used to refer to any agent for which at least some inference of carcinogenicity is available.

The adoption of hazard identification as the means of characterizing carcinogenicity determines that potency is not addressed as a specific parameter. For a given agent, indications of potency, or relative potency, may be inherent in the data allowing for hazard identification, but such information is not separately taken into account to adjust the absolute or relative level to which an agent(s) is categorized.

3.2. Evidence of exposure

While categories for evidence of carcinogenicity can be specified by reference to hazard identification, no analogous system is immediately applicable in relation to evidence of exposure. However, the principle underpinning different categories of carcinogenic hazard, namely proximity to proof of causation of cancer in humans, may be applied. Circumstances of exposure can be categorized in relation to the certainty that particular circumstances are those in which cancer causation has been established to occur, or that such an outcome may, at best, be inferred, or is unknown or that there is evidence to the contrary.

Determination of an appropriate category for exposure evidence does not involve or depend upon the means by which

Table 1
Procedural basis for qualitative assessment of carcinogenic risk

Assessment is predicated on specification of a carcinogenic agent and particular circumstances in which humans are exposed. Evidence of carcinogenicity for the agent in question and the circumstances under which exposure occurs are then banded in relation to the following categories:

For carcinogenicity, according to whether current evaluation of epidemiological, experimental, mechanistic and other data indicate

1. Recognized carcinogen for humans: definitive evidence of causality
2. Probably carcinogenic for humans: causality not definitive but otherwise substantive evidence
3. Possibly carcinogenic for humans: causality cannot be reasonably excluded
4. Inadequate evidence of carcinogenicity: the agent cannot be reasonably assigned to any of the above categories
5. Probably not carcinogenic for humans

For exposure, according to whether biological (tissue levels, excretion, molecular or cellular alteration), environmental (atmospheric concentration, etc.) or inferential (location, job description) data indicate

1. Exposure in circumstances which serve to establish the agent in question is a recognized carcinogen
2. Exposure circumstances which contribute in part to establishing carcinogenicity status for the agent involved
3. Exposure in circumstances distinct from those providing clearest evidence of carcinogenicity for the agent involved
4. Exposure in circumstances not characterized in relation to carcinogenicity (that is not able to be allocated to categories 1–3 above)
5. Circumstances of exposure identifiable with evidence for lack of a carcinogenic effect

By reference to categories accorded to carcinogenicity and exposure data, risk is allocated as

α -Band risk—*proven carcinogenic outcome*

Exposure to a recognized carcinogen in circumstances establishing carcinogenicity status

β -Band risk—*likely carcinogenic outcome*

β 1: Exposure to a probable carcinogen in circumstances which contribute to establishing carcinogenicity status

β 2: Exposure to a recognized carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity

β 3: Exposure to a probable carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity

γ -Band risk—*inferred carcinogenic outcome*

γ 1: Exposure to a possible carcinogen in circumstances which contribute to establishing carcinogenicity status

γ 2: Exposure to a possible carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity

γ 3: Exposure to an agent having inadequate evidence of carcinogenicity in circumstances about which particular data suggest increased risk

δ -Band risk—*unknown carcinogenic outcome*

Any circumstance of exposure to an agent having inadequate evidence of carcinogenicity

ϵ -Band risk—*unlikely carcinogenic outcome*

Exposure to an agent having possible or inadequate evidence of carcinogenicity in which lack of a carcinogenic effect is often observed

exposure is determined. Relevant evidence may include analysis of tissues, bodily fluids or excreta [27]. Exposure may have been determined by use of personal monitoring devices or detection of the agent in the immediate environment (air, water, food, etc.) of particular individuals. Exposure may be inferred from job description or details of occupational hygiene, or on the basis of acknowledged or inferred use of a consumer product, or from geographical location of residence or similar identifier. Inference of exposure may also be made from the known physical or chemical properties of the agent under consideration. These various parameters are relevant to the strength of evidence of exposure. Strength of relevant evidence is independent of the exposure category deemed most appropriate for a particular situation.

The highest category (evidence of exposure, level 1 in Table 1) is synonymous with those circumstances of exposure that have been the basis of epidemiological studies establishing carcinogenicity of certain agents unequivocally. Level 2 exposure is indicated by circumstances which provide epidemiological evidence that does not, when considered in isolation, establish that the agent under investigation is a recognized carcinogen. Typically, level 2 may involve exposure to a carcinogen at lower levels than those primarily establishing that agent's carcinogenicity status because, for example, of

greater geographical remoteness of the population studied from where the agent is produced, used or emitted.

Circumstances of exposure at levels 3–5 involve degrees of uncertainty in relation to cancer causation. Level 3 accommodates circumstances of exposure distinct in some aspect from those providing evidence of carcinogenicity for the agent involved. Level 3 includes, but is not restricted to, a different route of exposure to that providing clearest evidence of carcinogenicity. Level 4 is provided to address circumstances of exposure not reasonably accommodated by levels 1–3. This level primarily includes circumstances of exposure which are entirely novel to the extent that there is no evidence relating the exposure in question to a carcinogenic outcome in some wider context.

Level 5 involves circumstances of exposure identified with lack of a carcinogenic outcome. This category might appear to be the simple counterpart to 'lack of carcinogenicity' (Table 1), but the analogy is not straightforward. In the context of carcinogenic hazard identification, provision for an agent being categorized as not carcinogenic for humans, is reasonable at first glance. However, the category has proved to be impracticable. With reference to IARC evaluations specifically, Group 4 ('probably not carcinogenic for humans') is of no import because agents must exhibit some evidence of

carcinogenicity as a condition for inclusion in the *Monograph* program [8]. ‘Some evidence’ – whatever it is – essentially precludes Group 4. More generally, a broad assertion concerning lack of carcinogenicity for an agent is rarely employed. Such an assertion carries the implications that no carcinogenic outcome will be observed irrespective of the circumstances of exposure and that any positive evidence of carcinogenicity may be discounted. In contrast, the identification of a specific mode of exposure to an agent as being associated with no evident increased risk of cancer is a more circumscribed evaluation and one that is often realized.

3.3. Risk bands

Qualitative risk assessment for a particular situation follows directly from categorization of the relevant evidence of carcinogenicity and evidence of exposure and is expressed in terms of the likelihood of a carcinogenic outcome. The general term ‘band’ has been adopted to refer to the various risks which may be defined. This terminology specifically avoids reference to ‘categories’ and possible confusion with terminology used by authorities such as IARC for hazard identification. Risk assessment for a situation is indicated by allocation within one of five bands: corresponding to (in order of decreasing risk) *proven*, *likely*, *inferred*, *unknown* and *unlikely carcinogenic outcome*. Some of these are further divided into sub-bands as shown in Table 1. Italicized terminology is used to indicate when these words are being employed in a defined context, because these adjectives (likely, unknown, etc.) will often be otherwise used in normal context. For ease of specification, particularly in relation to sub-bands, Greek letters (α , β , etc.) have been adopted for the bands. Thus, for example, a *likely carcinogenic outcome* occurs when exposure is to a probable carcinogen in circumstances which contribute to establishing carcinogenicity status (β 1) or to a recognized carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity (β 2) or to a probable carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity (β 3).

3.3.1. α -Band risk—*proven carcinogenic outcome*

This band is defined by a single combination of evidence of carcinogenicity and evidence of exposure: level 1 in relation to each determination (Table 1). The band identifies situations in which increased incidence of cancer has been causally associated with exposure to a carcinogen. The situations so identified were the vehicle for establishing carcinogenicity status; that is, the agent in question is a recognized carcinogen because of the various situations specified. In each such situation, at least some of the major tumour types are established, though the possibility of additional tumour types being identified is certainly not excluded, and may well be a most likely scenario.

In a level 1 circumstance of exposure to a recognized carcinogen, carcinogenic risk will depend on dose and will usually have been demonstrated to vary accordingly within a certain range (a dose–response). At levels of exposure below

such a range, not every situation encompassed by the descriptions used to identify α -band risk can be equated with certainty regarding disease causation.

3.3.2. β -Band risk—*likely carcinogenic outcome*

As enumerated in Section 3.3, this band encompasses three combinations of evidence of carcinogenicity and evidence of exposure. Circumstances of known exposure to a recognized or probable carcinogen are involved. For the sub-bands β 2 and β 3, some evidence consistent with an increased carcinogenic risk in the context of the situations involved may be available, but the carcinogenicity status of the agent (as a recognized or probable carcinogen) depends primarily upon other circumstances of exposure. In all instances, it is the nature of the evidence rather than any direct or implicit quantitation of risk, that allows the situations specified to be in the same band. By definition, these various circumstances of exposure to either a recognized or a probable carcinogen are deemed to present a *likely* risk. When available, quantitative assessment may establish that a particular situation presents a risk sufficiently low as to present no public health concern.

3.3.3. γ -Band risk—*inferred carcinogenic outcome*

In respect of the categorization of evidence of carcinogenicity and exposure, γ -band risk principally concerns situations involving exposure to a possible carcinogen. Such risk is identified with an *inferred carcinogenic outcome*. The corresponding sub-bands include those involving exposure to a possible carcinogen in circumstances the investigation of which is addressed in the corresponding hazard identification (γ 1) and exposure to a possible carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity for the agent involved (γ 2). Agents categorized as possible carcinogens are mainly those many substances found to be carcinogenic in experimental animals, concerning which there is no epidemiological data and about which there is scant or no knowledge of the mode/mechanism of action.

Known exposure to many such agents is restricted to particular workplaces or job descriptions, but exposure to a minority of workplace agents may occur in other contexts.

Where situations allocated to either the β - or the γ -band have been subject to epidemiological investigation, it follows that such studies (considered overall) do not provide clear evidence of increased risk. As is generally recognized, such failure to demonstrate increased risk is not indicative of the absence of risk. In the context of ordering the evidence as described here, the failure to demonstrate increased risk does not provide a basis for allocation to a “lower” band.

Also allocated to the γ -band are situations involving exposure to an agent reasonably identified as having inadequate evidence of carcinogenicity, but for which information suggesting increased risk is available in regard to a particular circumstance of exposure (γ 3). Such situations are allocated to γ 3 despite the consideration that different modes of exposure to the same agent may be characterized as presenting an *unknown carcinogenic outcome*.

3.3.4. δ -Band risk—unknown carcinogenic outcome

Use of italics to specify outcome is most readily justified in relation to this band. The criterion for allocation to the δ -band is not that evidence is equivocal or falls short of that required for other bands. *Unknown carcinogenic outcome* is not primarily intended to indicate those situations which have been identified in the media (for example) but have not apparently been the focus of investigation. Situations allocated to *unknown carcinogenic outcome* are restricted to those involving some circumstance of exposure to an agent for which there is inadequate evidence of carcinogenicity. Granted specification of exposure circumstances involving a probable or possible carcinogen, the issue of whether cancer will arise may be not established, leading to ‘unknown’ being applied. Such situations would either be allocated to the β - or γ -bands, or to the ε -band if lack of cancer causation is specifically evident.

3.3.5. ε -Band risk—unlikely carcinogenic outcome

Assessment of an *unlikely carcinogenic outcome* (ε -band) requires exposure to an agent having possible or inadequate evidence of carcinogenicity in circumstances without carcinogenic effect. In common with all other risk bands, this one is adopted not simply because it involves the combination of two categories of evidence (level 3 or 4 for carcinogenicity and level 5 for exposure in this instance), but also because once defined, specific situations can be exemplified.

Considered in the absence of examples to which the risk bands respectively refer, a fundamental difference may be perceived between *proven*, *likely*, *inferred* and *unknown* on the one hand and *unlikely* on the other: the former all involve degrees of positivity while the latter is negative. To differentiate the negative from what is uncertain or positive might prompt adoption of omega, rather than epsilon, to label this band. However, review of the evidence indicates that there is no such clear demarcation. Indeed, the ε -band represents a continuum with, rather than a quantum leap from, other findings. This continuum also provides the explanation for the relatively few situations indicative of an *unlikely carcinogenic outcome*. Essentially, situations allocated to the ε -band were investigated because of the perception that a carcinogenic outcome might be revealed. Thus, although IARC evaluations includes *Group 4—the agent is probably not carcinogenic to humans*, only a single substance has been so categorized. Assessment of a situation as being associated with an *unlikely carcinogenic outcome*, is far from a theoretical notion. The requirement for negative data for a single mode of exposure is inherently less challenging than categorizing a substance (for which some evidence of carcinogenicity exists) as not causing cancer in any circumstances.

4. Exemplary qualitative risk assessments

4.1. Limitation to situations in developed countries

To assess practicability, qualitative risk assessment according to the criteria specified (Table 1) has been undertaken in

respect of more than 50 situations. With reference to the risk bands which have been defined, the range covered by these situations is broad. However, the situations considered have been restricted to, and are understood, as they variously exist in developed countries. In applying this restriction, the priority that should be accorded to cancer control in developing countries is acknowledged [28]. Active smoking is one risk factor common to both developed and developing countries, but even this risk factor operates in a distinctive context when developing countries are considered [29]. Generally, causes of cancer in developed and developing countries are markedly different [30].

Differences between the circumstances of carcinogenic risk in developed and developing countries are particularly marked when specific carcinogens are considered. Avoiding dietary aflatoxins constitutes a major opportunity for cancer control in developing countries [31], but exposure to aflatoxins is addressed as a regulatory food standard in developed countries [32] and is not recognized for its potential to reduce cancer incidence. Arsenic contamination of drinking water causes cancer in Taiwan, Chile, Argentina and Bangladesh, but arsenic is not such a causative agent in Europe and North America [33]. Data from developing countries are critical to establishing that arsenic contamination of drinking water presents a carcinogenic hazard, but that consideration is not the issue constraining the present risk assessment. The issue is that if a worldwide perspective were taken, then in relation to arsenic in water for example, it would be necessary to address the risks posed for very many and differing populations all over the world. Circumstances of local pollution and occupational exposure to carcinogens differ between developed and developing countries, and differ between developing countries [34–36]. Clearly, many situations of concern involving exposure to environmental carcinogens in developing countries are not unknown in developed countries [37,38]. However, to address all major exposure situations to multiple carcinogens worldwide is not tenable. Situations considered have been restricted to those in developed countries.

4.2. Tabulation of relevant data and outcomes

Tables 2–6 summarize assessments made for various situations grouped according to each of the five *carcinogenic outcomes* (α - to ε -bands). Even though restricted to developed countries, the situations addressed in the Tables are exemplary rather than comprehensive. Indeed, because multiple modes of exposure to an unrestricted number of agents may be envisaged, a comprehensive listing of situations is not possible.

In the tables, the column ‘persons exposed’ indicates the population or group for whom exposure data are considered. For each situation, a ‘Carcinogen’ is specified. In reference to γ - to ε -bands (Tables 4–6), the heading is ‘Presumed carcinogen’ to indicate that in some situations, the carcinogenic agent has not been unequivocally established. For each carcinogen specified, the current hazard identification made

Table 2
Examples of α -band risk—*proven carcinogenic outcome*

Situation and references ^a	Persons exposed	Carcinogen	IARC/NTP listing ^b	Principal route(s) of exposure	Target organ (or tumour type)	Comment ^c
People smoking tobacco [156]	Active smokers	Tobacco smoke, being a mixture containing polycyclic aromatic hydrocarbons and the nitrosated derivatives of nicotine and nor-nicotine	1/A	Inhalation	Lung, oral cavity, naso-, oro- and hypopharynx, nasal cavity and paranasal sinuses, larynx, stomach, esophagus, pancreas, liver, kidney, ureter, urinary bladder, uterine cervix and bone marrow	Major preventable cause of malignant disease
People who previously smoked tobacco [156–158]	Ex-smokers	Tobacco smoke (as above)	1/A	Previous inhalation	As above	Risk is reduced by comparison with continued smoking
Using smokeless tobacco [159,160]	Users of snuff, chewing tobacco and snus	Tobacco-related nitrosamines	1/A	Oral	Oral cavity, pancreas	Animal data establish role of nitrosamines
Treatment with certain therapeutic drugs [161–165]	Patients receiving relevant drugs/treatments	Phenacetin-containing analgesics	1/A	Therapeutic administration	Target organ/tumor types specific for particular drug and include leukaemia and cancers of breast, liver, kidney and multiple other sites	Listed agents exemplify, but do not include all therapeutic drugs in the highest IARC/NTP category. Risk-benefit consideration are relevant; some drugs listed are used because of clear benefit despite a recognized hazard
		Diethylstilboestrol	1/A			
		Cyclophosphamide and other cytotoxic drugs (including combinations)	1/A			
		Combined estrogen-progestogen contraceptives	1/A			
Drinking alcoholic beverages [166,167]	Consumers of alcoholic beverages, and particularly those who smoke	Alcoholic beverages; (no class of drink is more markedly implicated than others)	1/A	Oral	Oral cavity, esophagus, liver, breast	No particular category of beverage (beer, wine or spirits) is most strongly implicated
Occupational cancer attributable to specific agents [109,123,168–170]	Workers handling, or having contact with, particular chemicals or radiation	Soot and tar	1/A	Dermal, inhalation	Target organ depends on the agent: most commonly lung, urinary bladder and skin; all sites combined for TCDD	Agents listed are only a subset of known occupational carcinogens. Agents listed are implicated in a non-occupational environmental context addressed in Table 3
		Benzo[<i>a</i>]pyrene	1/B	Inhalation		
		Asbestos	1/A	Inhalation		
		Vinyl chloride	1/A	Inhalation		
		Ionizing radiation	1/A	Inhalation		
		Radon	1/A	Irradiation		
		Benzene	1/A	Irradiation		
		Cr VI, Ni, As and Cd compounds	All 1/A	Inhalation		
		TCDD	1/A	Inhalation		
		Formaldehyde	1/B	Inhalation		

Deliberate exposure to sunlight [171]	White skinned populations	Solar radiation; broad spectrum ultraviolet radiation	1/A	Irradiation	Skin (cutaneous melanoma, squamous cell carcinoma, basal cell carcinoma) Lung and other sites	Account must also be taken of the beneficial effects of sunlight in relation to vitamin D By comparison with occupational cancers caused by particular agents, specific causative agents have not been identified in relation to the work environments listed
Particular work environments or job classifications [95,108,122,130]	Workers, e.g. work as a painter and work in the rubber industry; environments associated with aluminium production, coke production, furniture and cabinet making; iron and steel founding	Some chemicals implicated (e.g. exposure to polycyclic aromatic hydrocarbons or aromatic amines) but causality not established because of complex exposures	One for all workplace exposures specified. (NTP does not evaluate workplace exposures)	Inhalation, and in some instances, dermal		
Residing near point sources of recognized carcinogens causing extreme local pollution [109,110,172–174]	Relevant local populations	Asbestos Coke oven and iron foundry emissions Arsenic, cadmium and nickels compounds	1/A 1/A 1/A	Inhalation in all cases	Lung and other sites depending on pollutant	Studies indicate increased cancer risk in local populations, though some studies fail to establish carcinogenic risk in this context
Passive smoking [156]	Children and adults in smoker household; persons exposed as a consequence of smoking in the workplace and other environments	Tobacco smoke passively inhaled	1/A	Inhalation	Lung. Some evidence regarding larynx and other sites	Some inferences in relation to target organs apart from lung (e.g. larynx)
Drinking water contamination from industrial sources of arsenic [109]	Surrounding communities	Arsenic compounds	1/A	Ingestion	Urinary bladder and others	Many relevant studies do not established increased incidence of cancer despite clear evidence of relevant exposure
Residential exposure to radon [175,176]	Occupants of particular houses	Radon	1/A	Inhalation and irradiation (yes: studies involving home exposure indicate causality)	Lung	Carcinogenic hazard established primarily by occupational studies but residential risk is specifically recognized

Exposure to a recognized carcinogen in circumstances establishing carcinogenicity status.

^a References cited are limited to recent or key studies through which a wider spectrum of relevant information may be accessed.

^b Listings are given at the respective websites <http://monographs.iarc.fr> and <http://ntp.niehs.nih.gov/ntp/roc/toc11.html> which also provide access to comprehensive documentation concerning particular carcinogens by IARC and NTP.

^c Information provided is considered to be generally applicable, but circumstances which amount to an exception to the comment may have been published, and this possibility may warrant a specific search.

Table 3
Examples of β -band risk—likely carcinogenic outcome

Situation and references ^a	Persons exposed	Carcinogen	IARC/NTP listing ^b	Principal route(s) of exposure	Likely target organ (or tumour type) ^c	Comment ^d
β1: Exposure to a probable carcinogen in circumstances which contribute to establishing carcinogenicity status						
Occupational cancer reasonably attributable to specific agents [105,177–180]	Relevant workers	Trichloroethylene	2A/B	Inhalation and dermal	Liver, biliary tract	Compounds specified are occupational hazards which also have an environmental impact
		Polychlorinated biphenyls	2A/B	Inhalation	Liver, biliary, others	
		Acrylamide	2A/B	Inhalation and dermal	Pancreas	
		Diesel exhaust	2A/B	Inhalation	Lung	
Particular workplaces, job classifications or occupational environments [39,181–184]	Workers undertaking various occupations	Not identified; risk related to work environment: e.g.		Implicitly inhalation and dermal exposure, but clear specification not possible		Consult IARC Group 2A ‘Exposure Circumstances’
		Hairdressing	2A		Urinary bladder, NHL	Examples cited have implications relating to non-work exposures
		Petroleum refining	2A		Skin cancer, leukaemia	
Work using insecticides apart from arsenic-containing compounds [113,115,185]	Workers manufacturing and applying insecticides	Occupational exposure to multiple insecticides	2A	Dermal and inhalation	Lung, multiple myeloma, NHL	No single agent has been shown to predominately account for risk
Local atmospheric pollution from point sources of industrial emissions [96,186–189]	Residents of particular local communities	Multiple, often unspecified, from petrochemical, steel and other industry		Inhalation	Lung	Attributing risk to specific agents is inherently difficult
General atmospheric pollution (excluding tobacco smoke) [190,191]	Whole population	Pollutants include		Inhalation	Lung	Quantitative assessment is required to adequately characterize risk in differing locations
		Diesel exhaust	2A			
		Gasoline exhaust	2B			
		Sulphur dioxide	3			
Tanning through sunlamps and solaria [192,193]	Persons using the appliances	Ultraviolet radiation	2A	Irradiation	Skin	Sunlamp data plus carcinogenic hazard established in relation to solar irradiation
Smoking marijuana [194,195]	Smokers of marijuana	Smoke contains polycyclic aromatic hydrocarbons and other compounds		Inhalation	Lung	Currently available data do not clearly establish causality
β2: Exposure to a recognized carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity						
Occupational exposure to cytotoxic drugs [196,197]	Oncology nurses and pharmacists	Cyclophosphamide and conventional cytotoxic drugs	1/A	Inhalation and dermal	Not clear; no direct evidence	Evidence of exposure and inference of biological effects (reduced birth numbers)
Prenatal exposure to tobacco smoke [198]	Children whose mothers smoke during pregnancy	Tobacco smoke	1/A	Transplacental	Leukaemia	One of a many environmental pollutants implicated in epidemiological studies of childhood cancer
Formaldehyde emitted from building products [199]	Occupants of relevant buildings	Formaldehyde	1/B	Inhalation	Nasopharynx and associated cavities	Formaldehyde considered an indoor air pollutant

Table 3 (Continued)

Situation and references ^a	Persons exposed	Carcinogen	IARC/NTP listing ^b	Principal route(s) of exposure	Likely target organ (or tumour type) ^c	Comment ^d
Cancer attributable to preserved timber in playgrounds [52,200]	Children primarily	Copper chrome arsenate	1/A	Ingestion, dermal absorption of As/Cr compounds	Not clear	Direct evidence of exposure
Contamination of food by vinyl chloride [201]	Whole population	Vinyl chloride	1/A	Ingestion	Angiosarcoma primarily	Monomer detected in some foods
Benzene contamination of specific food or drink products [202]	Whole population	Benzene	1/A	Ingestion	Not clear	Unacceptable food contamination by a recognized carcinogen
Living near a properly operating nuclear facility [127,203,204]	Local community	Ionizing radiation	1/A	Irradiation	Leukaemia, breast, thyroid	Very low incidence of occupational disease
Asbestos in drinking water [128,205]	Particular communities	Asbestos	1/A	Ingestion	Colo-rectum and possibly other sites	Inference of hazard from bioassay data
Contamination of food by aflatoxins in developed countries [32]	Whole population	Aflatoxins	1/A	Ingestion	Liver	Routine monitoring to prevent contamination
β3: Exposure to a probable carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity						
Environmental contamination by polychlorinated biphenyls [131,206]	Whole population	Polychlorinated Biphenyl congeners	2A/B	Inhalation, dermal	NHL	Levels in tissues and bodily fluids falling over time
Eating TCDD-contaminated food [50]	Specific populations, particular families of fishermen	TCDD	1/A	Ingestion	Not clear; possibly all cancer combined	Mode of exposure distinct from disaster or occupational exposure
Living near waste incinerator [207,208]	Specific local populations	TCDD	1/A	Inhalation, oral	All cancer combined	Marked reduction in TCDD exposure in developed countries during last 2 decades
Living near a contaminated site, apart from circumstances involving arsenic contaminated water supply [97,209–211]	Surrounding community	Pollution often involves multiple chemicals including heavy metals, polychlorinated biphenyls, dioxins, solvents and others		Inhalation and possibly dermal	Liver and possibly other sites	In the absence of increased cancer incidence, inference of exposure and harm may be evident from, for example, decreased birth weight
Acrylamide in (deep fried) food [76,77,212]	Consumers of particular products and possible whole population	Acrylamide	2A/B	Oral	Colo-rectum	Altered of food processing to minimize contamination, regard-less of cancer detection
Nitrosamines in beer, cured meats and other food [72,213,214]	Persons eating relatively large amounts of processed meat	N-nitrosodimethyl-amine and possibly other N-nitroso compounds	2A/B	Ingestion	Stomach, and possibly other sites	Bioassay & metabolism by human tissue provide unequivocal evidence of hazard
Leaching of fire retardant from children's sleep ware [215]	Infants	Tris(2,3-dibromopropyl) phosphate	2A/B	Dermal and oral	Not clear	Direct evidence of absorption from clothing

^a References cited are limited to recent or key studies through which a wider spectrum of relevant information may be accessed.

^b Listings are given at the respective websites <http://monographs.iarc.fr> and <http://ntp.niehs.nih.gov/ntp/roc/toc11.html> which also provide access to comprehensive documentation concerning particular carcinogens by IARC and NTP.

^c Specification of likely target organ is made in the absence of definitive knowledge and on the reasonable inference drawn from studies of other modes of exposure to the carcinogen in question and/or tumors assessed in relevant investigations.

^d Information provided is considered to be generally applicable, but circumstances which amount to an exception to the comment may have been published, and this possibility may warrant a specific search.

Table 4
Examples of γ -band risk—*inferred carcinogenic outcome*

Situation and references ^a	Persons exposed	Presumed carcinogen	IARC/NTP listing ^b	Principal route(s) of exposure	Likely target organ (or tumour type) ^c	Comment ^d
γ1: Exposure to a possible carcinogen in circumstances which contribute to establishing carcinogenicity status						
Occupational exposure to chemicals for which some evidence of carcinogenicity is available [102,104,125,216,217]	Various specific workers	Occupational exposure in dry cleaning Work involving Acrylonitrile Chloroform DDT	2B 2B/B 2B/B 2B/B	Inhalation and possibly dermal	Lung & other sites including leukaemia	Following exposure to many agents, attributing risk to single agents, most of which are categorized as possibly carcinogenic to humans, is difficult
Agricultural work involving herbicides [116,117,218]	Farmers, forestry workers	Chlorophenoxy and possibly other compounds	2B	Inhalation and dermal	Lymphoma	Lymphoma risk associated with agricultural work rather than specific chemicals
Residential exposure to insecticides. [98,219,220]	Occupants of sprayed houses	Many including chlordane	2B	Inhalation and dermal	Breast and various sites investigated	Increasingly better indicators of exposure are being used
Environment exposure to DDT [74]	Young women	DDT	2B/B	Not clear	Breast	Exposure determined by levels of DDT in serum
Heterocyclic amines in cooked meat and fish [221,222]	Whole population	Multiple compounds including PhIP	2B/B	Ingestion	Colo-rectum, prostate and possibly other sites	Impact of specific chemicals as mediating dietary-associated risk is difficult to resolve
γ2: Exposure to a possible carcinogen in circumstances distinct from those providing clearest evidence of carcinogenicity						
Chloroform in toothpaste [223]	Consumers of the product	Chloroform	2B/B	Ingestion	Not clear	Usage discontinued in many countries
Polybrominated biphenyls as flame retardant [224,225]	Children primarily and otherwise, whole population	Polybrominated biphenyls	2B/B	Oral and dermal exposure of infants	Not clear	Relatively new compound Blood levels rising in general US population
Contaminated honey [226]	Consumers of the product	Pyrrolizidine alkaloids	2B	Ingestion		Dietary intake of extremely low concentrations
Pollutants and pesticide residues in breast milk [227–229]	Infants	Various pesticides, polychlorinated Bipenyls TCDD	2B 2A/B 1/A	Oral exposure of infants	Not clear	Infants considered to be a most vulnerable population. Compounds may be detectable long after usage ceases
Personal use of hair coloring agents [75,230,231]	Users of hair dyes (predominantly women)	Not clear; dye formulations subject to change over time		Dermal	Hematopoietic neoplasms Urinary bladder	Evidence of dye absorption
Environmental exposure causing childhood leukemia [232–235]	Children	Multiple pollutants implicated		Main route not clear, but presumably including inhalation, oral and dermal	Leukaemia	Relevant environmental exposures also include infection-related risk factors
γ3: Exposure to an agent having inadequate evidence of carcinogenicity in circumstances about which particular data suggest increased risk						
Residence near power lines [236–238]	Children	Extremely low frequency electric and magnetic fields	2B	Irradiation	Leukaemia	Causality not established but reported associations cannot be discounted
Perineal use of talc-based body powder [241]	Women using body powder	Talc used in this manner	2B	Retrograde absorption via reproductive tract	Ovary	Not supported by relevant experimental findings

^a References cited are limited to recent or key studies through which a wider spectrum of relevant information may be accessed.

^b Listings are given at the respective websites <http://monographs.iarc.fr> and <http://ntp.niehs.nih.gov/ntp/roc/toc11.html> which also provide access to comprehensive documentation concerning particular carcinogens by IARC and NTP.

^c Target organs subject to speculation or inference only.

^d Information provided is considered to be generally applicable, but circumstances which amount to an exception to the comment may have been published, and this possibility may warrant a specific search.

Table 5
Examples of δ -band risk—*unknown carcinogenic outcome*

Situation and references ^a	Persons exposed	Presumed carcinogen	IARC/NTP listing ^b	Principal route(s) of exposure	Suspected target organ (or tumour type) ^c	Comment ^d
Medical management involving blood transfusion bags and similar devices [239,240]	Persons subject receiving blood or similar products	Di(2-ethylhexyl) phthalate	3	Systemic	Not clear	No clear indication of risk despite evidence of exposure
Occupational exposure to agents with inadequate evidence of carcinogenicity [241–244]	Workers involved	Talc not containing asbestos	3	Dermal and inhalation	Lung	Listing of agents in this category is limited here to agents implicated in other environmental contexts
		Gasoline exhausts	3	Inhalation	Lung	
		Atrazine	3	Inhalation and dermal	NHL or other sites	
Consuming chlorinated drinking water [245,246]	Whole population	Chlorinated drinking water	3	Ingestion	Urinary bladder, colo-rectum and some other sites investigated	Unequivocal evidence of the benefit of chlorination must be considered
		Dichloroacetic acid	2B			
		Chloroform	2B/B			
		Other products	3			
Hazard presented by cell (mobile) phones [247–250]	Cell (mobile) phone users	Electromagnetic fields	3	Irradiation	Brain	Risk associated with long term use remains to be established
Consuming aspartame [129,251,252]	Consumers of relevant foodstuffs	Aspartame	3	Oral	Bladder or other sites	Despite negative epidemiology, fetal exposure may be a risk
Environmental exposure to atrazine [253,254]	Women living in certain regions	Atrazine		Oral, inhalation	Breast	Widespread exposure
Non-occupational exposure to solvents [255]	Persons variously using solvents	Multiple agents		Inhalation	NHL	Limited number of specific studies
Agent in non-stick cookware and breathable all-weather clothing [256]	Relevant consumers	Perfluorooctanoic acid		Ingestion	Not clear	Concern addresses multiple possible adverse effects apart from cancer
Environmental pollutants, including xenoestrogens, increasing risk of breast cancer [91,120,257,258]	Women in whole population	Various insecticides and pollutants		Presumably inhalation; priority exposure not established	Breast and other sites	Available data do not allow discrimination between multiple agents to indicate greatest harm
Use of irritant cosmetics [259]	Women who use the product	Sodium lauryl sulfate		Dermal	Not clear	No clear indication of risk
Food additives [260,261]	Whole population	Many compounds including alitame, sodium carboxy-methyl cellulose, nitrite		Ingestion	Not clear but presumed to include colo-rectum	Review of the data indicates little increased insight of late although issue has been addressed for decades
Using products containing bisphenol A [262,263]	Entire community in light of the wide range of consumer products	2,2-Bis(4-hydroxy-phenyl)propane		Ingestion and possibly other routes	Not clear	Inference of hazard from studies of spontaneous abortion and prostate cancer relapse

Any circumstances of exposure to an agent having inadequate evidence of carcinogenicity.

^a References cited are limited to recent or key studies through which a wider spectrum of relevant information may be accessed.

^b Listings are given at the respective websites <http://monographs.iarc.fr> and <http://ntp.niehs.nih.gov/ntp/roc/toc11.html> which also provide access to comprehensive documentation concerning particular carcinogens by IARC and NTP.

^c Target organs subject to speculation or inference only.

^d Information provided is considered to be generally applicable, but circumstances which amount to an exception to the comment may have been published, and this possibility may warrant a specific search.

Table 6
Examples of ϵ -level risk—*unlikely carcinogenic outcome*

Situation and references ^a	Persons exposed	Presumed carcinogen	IARC/ NTP listing ^b	Principal route(s) of exposure	Suspected target organ (or tumour type) ^c	Comment ^d
Consuming artificial sweeteners (apart from aspartame) [264,265]	Diabetics; consumers of 'diet' drinks and food	Saccharin cyclamate	3, 3	Oral	Bladder; possibly other sites	Epidemiological data discount concerns arising from animal studies
Coffee drinking [266–268]	Adult population who consume coffee	No specific component of coffee clearly implicated	2B and 3	Ingestion	Urinary bladder, pancreas, stomach	Multiple studies indicating lack of carcinogenic risk
Using deodorants [269]	Consumers of the product	Alkyl esters of <i>p</i> -hydroxybenzoic acid		Dermal	Breast	Some studies indicating lack of risk; lack of risk inferred from other data
Drinking fluoridated water [270,271]	Whole population in particular regions	Sodium fluoride	3	Ingestion	Bone	Marked body of evidence indicating lack of risk
Occupational exposure to electromagnetic fields [272–274]	Electricity workers	Electromagnetic fields	3	Irradiation	Leukaemia, breast, brain	No consistent evidence of risk despite unequivocal evidence of exposure
Breast implants causing breast or other cancer [275–277]	Women with breast implants	Foreign body (silicone implant)	3	Intramuscular or intraglandular	Breast	Multiple studies indicating lack of evident risk
Dental fillings [278]	Most of the population	Dental amalgam	3	Ingestion, intradental	Oral cavity and possibly other sites	Evidence of lack of risk

Exposure to an agent having possible or inadequate evidence of carcinogenicity in which lack of a carcinogenic effect is observed.

^a References cited are limited to recent or key studies through which a wider spectrum of relevant information may be accessed.

^b Listings are given at the respective websites <http://monographs.iarc.fr> and <http://ntp.niehs.nih.gov/ntp/roc/toc11.html> which also provide access to comprehensive documentation concerning particular carcinogens by IARC and NTP.

^c Target organs subject to speculation or inference only.

^d Information provided is considered to be generally applicable, but circumstances which amount to an exception to the comment may have been published, and this possibility may warrant a specific search.

by IARC and NTP, if available, is shown in the column headed 'IARC/NTP listing'. Blanks in this column arise in part because NTP identifications do not include 'environmental exposures' and inevitably some such exposures are yet to be addressed by IARC [39]. Also, and as must be expected, some agents concerning which there is little or uncertain evidence of carcinogenicity, have not been evaluated by one of, or in some cases, by either IARC or NTP.

The 'Principle route(s) of exposure' refers to that described or implicit from the situation specified and with reference to studies undertaken. Where possible, 'Target organ' is specified. By definition, for *proven carcinogenic outcomes* (α -band risk), relevant target organs are established, and listed as such in Table 2. For lesser bands of risk (Tables 3–6), the corresponding column is headed 'Likely target organ' and differing degrees of uncertainty regarding this matter are indicated, including the consideration that the target organ is 'Not clear'. The 'Comment' column allows mention to be made of other relevant issues. Generalizations about particular carcinogens and/or circumstances of exposure are rarely of universal application. Accordingly, information provided under 'Comments' may not be of universal application and/or may require qualification to take account of local situations or particular categories of persons.

4.3. Derivative rather than *de novo* assessments

Qualitative risk assessment for any given situation, as described here, intrinsically depends upon hazard identification and other findings such as appraisals of data published as reviews. Accordingly, a qualitative risk assessments is derivative, and is arguably invalid if it is not consistent with relevant hazard identification and with quantitative risk assessment when available.

Risk assessments presented in Tables 2–6 do not purport to be based upon *de novo* appraisals for each of the more than fifty situations specified. Evaluations of carcinogenicity data are those adopted by IARC and/or NTP. Otherwise, the information presented for each situation is intended to reflect relevant reviews. In the absence of appropriate reviews, or complementing them, recent studies are cited because such publications provide multiple references to previously published work. There is no implication that any recent study is authoritative for that reason alone. Thus the innovation arising from Tables 2–6 is not the characterization of risk for any particular situation, but is the manner in which various situations present risks which are qualitatively similar on the basis of the criteria set out in Table 1. Well-recognized risks, such as those associated with tobacco are listed at the outset in Table 2 to indicate that they

have not been overlooked. Otherwise, situations covered in Tables 3–6 are randomly ordered within the various bands or sub-bands.

4.4. Taking account of mechanistic and other data

In hazard identification, understanding of the relevant mode and mechanism of action contributes critical insight [4,5]. Consideration of mechanism is consistent with a threshold in the case of 2,3,7,8-tetrachlorodibenzo-*para*-dioxin (TCDD) and similar chemicals [40,41]. With reference to IARC evaluations, Vineis and Perera [42] have recently tabulated over fifty chemicals and exposures subject to ‘upgrade’ or ‘downgrade’ on the basis of mechanistic data, change being relative to the classification nominally indicated by epidemiological and bioassay data considered in isolation. By far the most common scenario involved agents otherwise allocated to Group 2B (*possibly carcinogenic for humans*) being ultimately listed as 2A (*probably carcinogenic for humans*). Thus, mechanism of action has been addressed during IARC or comparable hazard identification of an agent, and will consequentially influence qualitative assessment of risks involving that agent through its effect on categorizing evidence of carcinogenicity. There is no requirement to separately specify a means to address mechanism or mode of action in the context of determining ‘Evidence of carcinogenicity’ (Table 1).

Beyond being addressed in the course of hazard identification, and hence influencing level in relation to evidence of carcinogenicity, mode or action or mechanistic data may be relevant to particular circumstances of exposure. A broad range of findings may be cited under this heading, and examples include the manner in which toxicokinetics are determined by a dietary route of exposure to acrylamide [43], the consideration that metabolites may indicate target organs for trichloroethylene [44], and DNA-protein crosslinks are attributable to occupational exposure to formaldehyde [45]. Changes in specific genes, exemplified by regional differences in pollution determining altered patterns of oncogene mutation [46] and p53 mutations determined by environmental tobacco smoke [47], have been documented with reference to various topographical sites and are recorded in multiple databases [48]. The scope of such data precludes the development of formularies to address mechanistic data systematically in the context of qualitative risk assessment. Mechanistic findings may be taken into account on a case-by-case basis or as indicators of reasonable comparability between situations otherwise allocated to the same risk band.

The scope of data relevant to exposure is burgeoning [49]. Such findings are often reported in the absence of information concerning carcinogenic risk. They obviously include biological data such as blood levels of dioxin-like chemicals in fisherman [50], but extend to clarifying circumstances of exposure otherwise established by inference. The latter are exemplified by whether proximity to crops is reasonably indicative of exposure to agricultural chemicals [51]; that children playing on chromated copper arsenate-treated timber should be regarded as being exposed to the preservative [52] or

that persons at risk from solariums (sunbeds) may include those nominally prohibited from accessing such services [53]. As concluded in relation to mode or mechanistic data, the scope of findings appears to preclude any systematic analysis, but such exposure data concerning a particular situation may indicate that a specific risk band is appropriate.

5. The utility of qualitative risk assessments

5.1. The generation of lists

The procedure for qualitative risk assessment used here (Table 1) is predicated on the assessment of individual situations. The outcome of such assessment does not inherently involve the generation of lists, but this cannot be excluded. Hence, the listing of situations allocated to the same band must be considered. Might such lists be confused with those arising from hazard identification as published by IARC or NTP [7,8]? This seems unlikely because there are immediate and obvious differences between hazard identification and qualitative risk assessment, some of which have been discussed (Section 2). Multiple differences between hazard identification and qualitative risk assessment emerge if, for sake of discussion, qualitative risk assessment is caricatured as a means of generating lists. Any such lists would be markedly different in character from those emerging through hazard identification (Table 7).

In qualitative risk assessment as outlined here, hazard identification is a required starting point and is therefore not the outcome. The process begins (Table 1) by reference to evidence of carcinogenicity as determined by IARC and/or NTP or, in the absence of such a determination, using criteria specified for that purpose by IARC and/or NTP or by noting that no such evidence is available concerning a particular agent. Other differences are noteworthy. Hazard identification listings are the cumulative outcome of multiple formal determinations. In common with quantitative risk assessment, a qualitative risk assessment may be made by any investigator in relation to one or more situations and published accordingly. It is not the prerogative of a recognized authority such as IARC or NTP.

5.2. The place of ‘workplace only’ carcinogens

Tables 2–6 often involve specific carcinogens being referred to more than once as each is specified in the context of differing circumstances of exposure. Exposures exemplified here are skewed toward those relevant to the wider community. However, some situations involving occupational exposure have been included to indicate context within the risk bands described. For these well-investigated occupational situations, risk bands are determined by whether the generally highest-known levels of occupational exposure involve agents which are recognized, probable or possible carcinogens. A further subset of situations, namely those in which differing jobs may involve exposure to lesser levels of a given carcinogen, exemplified by the extent to which auto mechanics or telephone

Table 7
Differences between ‘lists’ generated through hazard identification and qualitative risk assessment

Determinants and characteristics of listing	Hazard identification listings (IARC/NTP)	Qualitative risk assessment bands
Nature of individual entries	A particular agent (OR, less often and sometimes never) a circumstance of exposure	A situation specified in terms of an agent and circumstances of exposure to that agent
Scope of individual entries	Finite: restricted to the agents for which evidence of carcinogenicity is available	Unlimited: no limitation on the number of exposure circumstances which might be identified in relation to each agent
Number of times a particular agent may appear	Once	Multiple (will be once if there is only one known context of exposure)
Basis of listing within categories	Alphabetical using agent’s chemical or other technical name	None evident
Coverage of agents	Limited: many agents for which some inference of carcinogenicity is available will not be subject to hazard identification	Comprehensive: situations involving reasonable inference of carcinogenic risk are amenable to assessment irrespective of whether the agent(s) involved has been subject to hazard identification
Authority underpinning categorization	Explicit authority of IARC, NTP, etc.	Implicit authority through peer-review literature
Occasion for new entry	Only after evaluation (or re-evaluation) by relevant authority	<i>Ad hoc</i> on the basis of competent publication

linemen are exposed to asbestos [54,55], have not been addressed in the interests of a manageable document.

Also in the interests of a manageable document, specification of situations involving occupational carcinogens has been largely restricted to agents that are also encountered in one or more situations apart from the workplace. Accordingly, some hundreds of chemicals categorized by IARC and NTP as at least possibly carcinogenic to humans, and for which known human exposure involves only respective workplaces, are not included here. The absence of situations involving those chemicals could create the impression that exposure to carcinogens identified through animal bioassay is not addressed through the present approach to qualitative risk assessment. In formal terms this is not correct: evidence of carcinogenicity as addressed in Table 1 may involve experimental findings only. However, there is little to be gained, over that which is implicit from hazard identification, from qualitative risk assessment for agents known to be only encountered in the workplace. Distinguishing between such agents for the purpose of determining priorities requires quantitative risk assessment. In contrast, for carcinogens to which humans are variously exposed, banding of risk situations as shown in Tables 2–6 provides information additional to that which is available through hazard identification.

5.3. Inclusion of suspected carcinogens

In comparison with hazard identification, the present compilation of risk assessments involves some agents not currently listed by IARC or NTP, but agents for which some imputation of carcinogenic hazard may be made (see Tables 4 and 5 in particular). Qualitative risk assessment as presently undertaken, addresses at least partially, the relative priority reasonably accorded to risks presented by exposure to putative or suspected carcinogens. For many of the agents involved, an evaluation of carcinogenicity status is usefully delayed pending

publication of additional and more informative data. In the interim, a qualitative risk assessment may indicate that, on the basis of current scant evidence, the imputed risk is minimal when contrasted to that posed by well-characterized exposures to recognized carcinogens.

6. Matters affecting utilization of assessments

6.1. Not all risk factors addressed

In determining priorities for the development of cancer control measures, quantitative assessments which follow the precedent set by Doll and Peto [56] provide an overall perspective [30,57,58]. Cancer development in humans is usefully described with reference to the impact of exogenous carcinogens and endogenous factors [59]. Qualitative risk assessment as delineated here addresses risk consequent upon exogenous carcinogens, it being recognized that understanding of the term ‘carcinogen’ is continually evolving [60]. Complexity also attends the term ‘environment’ in the present context. Addressing this complexity, Boffetta et al. [61] note that ‘environment’ can encompass all non-genetic factors such as diet, lifestyle and infectious agents. All non-genetic factors obviously include the natural or man-made agents encountered by humans in their daily lives, exposure to which they have no or limited control. In relation to cancer, however, the term ‘environmental factors’ may also be understood to refer only to natural or man-made agents to which people are involuntarily exposed; relevant chemicals are essentially various categories of pollutants and substances encountered at work [62].

While acknowledging the disagreement that sometimes arises regarding quantitation of the cancer burden attributable to ‘environmental factors’ [63], an approach to quantitative risk assessment predicated on exogenous carcinogens does not address this issue. Exogenous carcinogens include those associated with lifestyle, such as tobacco smoking, excessive

alcohol consumption, or deliberate sun exposure and those to which individuals are involuntarily exposed such as occupational carcinogens and certain pollutants.

In concert with common usage, the term exogenous carcinogen as used here excludes a range of hormonal and reproductive factors and broad aspects of diet. Hence, cancer risk factors such as obesity [64], circadian rhythm [65], stress [66] and abortion [67] are not addressed. Likewise, the carcinogenic risk (or lack thereof) presented by carbonated soft drinks or chewing gum are not addressed because they are not a consequence of exposure to carcinogens; rather they are considered to involve increased gastro-oesophageal reflux and/or other physiological change [68,69]. Dietary risk factors such as fat content, total caloric intake or red meat content do not involve specific exogenous carcinogenic agents. Conversely, carcinogens present in food, as contaminants or otherwise (nitrosamines, aflatoxins, heterocyclic amines, etc.) are addressed. As a consequence, distinction is made, for example, between exogenous nitrosamines and endogenous nitrosation [70]. Such distinction between exogenous and endogenous factors is a corollary of procedure (Table 1). The distinction is made in the knowledge that there may well be a common carcinogenic process [71,72].

6.2. Assessments may vary with time

Allocation of situations to a particular risk band is wholly dependent on available data, and (apart from those involving a *proven outcome*) must be reviewed as new data are published. This particularly concerns categorizations of carcinogenicity in the context of hazard identification. *IARC Monograph* re-evaluations are prompted by new findings and often result in altered listings (in reference to Groups 1, 2A, 2B, etc.), as illustrated by the re-evaluation of formaldehyde [73]. Likewise, ‘Changed Listings’ are highlighted in successive NTP Reports on Carcinogens [7]. Although all authorities strive for timely review, listing accorded to any agent should always be subject to the possibility that more recently published data may allow additional insight.

The risk presented by a situation may vary with time as a consequence of alterations in the agent or circumstances of its usage [74,75]. Depending upon the context in which enquiry is made, distinction may be warranted between whether cancer causation has ever been demonstrated in a particular situation, and whether that situation, and any associated risk, is current. Thus the *IARC Monograph* on formaldehyde [73] notes that average levels of 0.5 mg/m³ or more have been measured in ‘mobile homes’, but these levels have declined since the late 1980s due to standards requiring that building materials emit lower concentrations.

Clearly, in relation to a recently described mode of exposure, recently published findings will be influential. Thus risk consequent upon acrylamide contamination of deep-fried food would warrant a different band if assessment were based wholly upon extrapolation from occupational exposure [76] and made prior to specific data regarding dietary exposure being available [77]. Recently published data concerning local conditions, if

available, may be taken into account when seeking to apply perspectives on risk based on general considerations [78].

6.3. Susceptibility

Whether an increased risk of cancer follows exposure to a carcinogen under particular circumstances may be determined, in part, by characteristics of the populations involved. Individuals at a life stage characterized by rapid growth and differentiation may be especially responsive to some carcinogens [79,80]. Investigation of the vulnerability of young women to dichlorodiphenyltrichloroethane (DDT) is predicated, in part, on this understanding [74]. Susceptibility amenable to specification by reference to a population – women environmentally exposed to DDT or children exposed to TCDD in breast milk – may be directly addressed by the procedure proposed (Table 1) by specifying the population at risk in the context of identifying the situation of interest.

Genetic determination of susceptibility specifically includes the impact of high penetrance genes, typified by the vulnerability of xeroderma pigmentosum patients to ultraviolet radiation [81]. For most people, however, individual susceptibility to particular carcinogens will be determined by low penetrance genes. These include genes that mediate carcinogen metabolism. Relevant findings establish important proof-of-principle, but have extremely limited clinical or public health application [82,83]. Susceptibility genes have been implicated in specific situations such as women who used hair dyes [75] or children exposed to indoor insecticides [84]. Single gene approaches to genetic determination of susceptibility (or any other phenotype) are being rapidly superseded [85]. Gene expression profiling of tumours is acknowledged as a determinant of prognosis and indicator of response to therapy, but also seems certain to play a role in understanding etiology, and thereby contributing to risk assessment [86].

From a qualitative perspective, present understanding of genetic determination of susceptibility may be aligned with hazard identification in that the matter involves the potential of an agent(s) to cause cancer irrespective of exposure circumstances. Accordingly, no provision has been made for the inclusion of genetic determination of susceptibility in the present protocol for qualitative risk assessment.

7. Parameters of carcinogenesis and their impact on assessments

7.1. Dose-related matters

As the dose of carcinogen increases, the carcinogenic effect, however recorded, is expected to increase [87]. Dose–response is determinative in quantitative risk assessment which, of necessity, must involve specification of a dose–response (see Section 2.2). The consideration that dose or level of exposure is not a specific parameter of the assessment procedure outlined here does not require or involve abrogation of this fundamental principle of cancer biology. Variation of risk according to level

of exposure may be examined either within a single situation or as it affects relationships between situations.

7.1.1. Variation of dose in the context of a single situation

There is no imputation that all individuals or populations encompassed by a particular situation will experience the same level of risk. Irrespective of the precision with which a situation entailing a carcinogenic risk is specified, some attenuation of risk must be anticipated consequent upon dose. Typically, within a dose range subject to investigation, variation in risk may be demonstrated. Below that range, risk may not have been determined but other considerations, including mode or mechanism of action may indicate that cancer causation cannot be discounted. Such qualifications in relation to a particular situation can be acknowledged and do not alter the nature of evidence indicating existence of risk. Using the present approach to qualitative risk assessment, attenuation of risk consequent upon reduced level of exposure can only be addressed by specification of a situation involving or limited to such relatively reduced level of exposure. This matter was alluded to earlier in relation to occupational exposure to asbestos (Section 5.2).

Obviously, not all circumstances pertaining to carcinogen dose can be addressed by specifying new situations indicative of exposure-related alteration in risk. A reason for adopting italicized terms (*proven, likely, etc.*) is to provide for use of these words to otherwise indicate variation in risk, without confusing that matter with the nature of evidence establishing risk. Thus circumstances coming within a situation allocated to the *proven* band may be considered to offer only an inferred risk of cancer causation due to a relatively low level of exposure. In the other direction, it must be emphasised that risks examined (Tables 2–6) are restricted to those in developed countries. The impact of sometimes massively higher pollution as it may occur in developing countries is often the subject for investigation [46,88–90]. Thus, for example, studies of an association of DDT with breast cancer conducted in North Vietnam, Mexico, Brazil and Columbia may be distinguished from those in USA as likely involving a population exposed to sprayed DDT versus those exposed via intake of residues in food [91]. Assessment of situations in developing countries may result in allocation to ‘higher’ risk bands than situations involving the same agents discussed here.

7.1.2. Dose with reference to different modes of exposure

If different circumstances of exposure to the same agent are described, those involving lesser levels of exposure are anticipated to result in lesser risk. The doses of carcinogen, received by various workers involved in studies establishing carcinogenicity of agents as occupational hazards in the first instance, are almost invariably greater than the doses affecting the corresponding local residential community [92]. Such localized exposure may be presumed to be greater than that experienced by the whole population. While such relationships can be generally expected, they cannot be presumed to be universal [93].

In examining the risks consequent upon differing circumstances of exposure to the same agents, variation in dose may

not be the only consideration. Differences between occupational, environmental and/or consumer exposure to the same agent may involve different routes of exposure. For example, environmental exposure to pesticides may particularly occur via water contamination [94], a scenario having little relevance to occupational exposure. Differences in route of exposure may have different outcomes and contribute to inconsistencies involving the same substance.

For a number of recognized carcinogens, including asbestos, polycyclic aromatic hydrocarbons, arsenic and certain heavy metals, decreasing levels of risk can be correlated with decreasing dose because distinct modes of exposure have been studied. This is evident in a progression through observations involving occupational exposure [95], the impact of point source pollution [96], residence near contaminated sites [97] and general environmental effects [24]. For several recognized carcinogens, this transition is indicated by α -band risk in respect of occupational exposure (Table 2) and β -band risk in relation to the impact of the same chemicals as environmental pollutants in various contexts (Table 3).

These progressive changes in risk might be reasonably hypothesised in respect of, for example, pesticides or organic solvents. However such chemicals have not been unequivocally established to cause cancer as a consequent of occupational exposure. Accordingly the relevant occupational risks are β - or γ -bands. Risks consequent upon lesser, that is environmental, exposures to these agents appear difficult to demonstrate and anomalies may occur. Thus, for example, there are indications of risk consequent upon residential exposure to chlordane specifically [98], although this particular pesticide is not implicated as pre-eminent in determining occupational risk [99,100].

7.2. Target organ

Concordance between experimental and epidemiological studies of cancer causation includes an understanding of target organ as a characteristic of carcinogens [6]. This is not to assert that a target organ evident in rodent bioassay indicates the likely target organ in humans exposed to the same agent. This is a complex and entirely different matter [101]. Indeed, for a given agent, target organs are generally particular to a strain or species of animals or to humans. Regarding the solvent dichloromethane, for example, liver and lung are major tumour sites indicated by rodent studies, while human (case control) studies have particularly concerned brain and breast tumours [102]. With respect to a given species, however, carcinogens are characterized by the preferential causation of tumours in one organ or group of organs, independent of dose. This principle may be qualified by reference to high-dose bioassay conditions where animals may die from high incidence/low latency tumours, thereby curtailing development of other cancers [87]. Likewise, high doses may also induce toxic injury and distort organ-specific metabolism, thereby affecting the site of tumorigenesis.

In bioassays using progressively lower doses of carcinogen, tumors consistently arise in the relevant target organs [103]. Correspondingly, in relation to human carcinogenic risk, a

recognized target organ may account for the design of a study. Particular tumor types may thus be designated as being ‘of *a priori* interest’ [104,105]. Weight reasonably accorded to slightly increased risk of cancer associated with relatively low exposure to a carcinogen is greatest when the relevant target organ is affected. Conversely, biological plausibility may be an issue when, after low level of exposure, increased risk of cancer involves an organ site not previously implicated. A possible exception, to the understanding of target organ, are those agents characterized as increasing the risk of ‘all cancers combined’ rather than the risk of a particular tumour type. For the purposes of examining consistency between studies, however, ‘all cancers combined’ may be regarded as a target organ.

Specification of target organ is not a required outcome from hazard identification, but it may be an element in evaluating the relevant data. Thus, for example, in evaluating the possible association between environmental exposure to lead compounds and lung cancer, the *IARC Monograph* specifies ‘these results within a low-dose population are not consistent with those for lung cancer in more highly exposed occupational populations’ [106]. In the *Monograph* on ‘Involuntary Smoking’ (involving a different Working Group) [107], breast cancer is largely discounted as an outcome. The *Monograph* specifies: ‘Finally, the lack of an association of breast cancer with active smoking weighs heavily against the possibility that involuntary smoking increases the risk for breast cancer, as no data are available to establish that different mechanisms of carcinogenic action operate at the differing dose levels of active and of involuntary smoking’.

7.2.1. Sometimes consistently observed

Across different situations listed in Tables 2 and 3, exposure to polycyclic aromatic hydrocarbons is associated with increased risk of lung cancer [108], arsenic with skin, lung, urinary bladder, kidney and liver cancer [109] and asbestos with mesothelioma [110]. Indeed such consistency essentially accounts for the jargon term ‘target organ’.

7.2.2. Less than consistent findings

By comparison with risks involving recognized carcinogens, risks consequent upon exposure to probable or possible carcinogens (Tables 3 and 4) are sometimes inconsistent when they are compared in relation to target organ. For example, occupational exposure to multiple pesticides is strongly associated with increased risk of lung cancer [99,111]. Studies concerning specific pesticides do not implicate this target organ [100,112]. Rather, non-Hodgkin lymphoma [113] and leukaemia [114] emerge, though chemical-specific findings are almost invariably based on small numbers and multiple comparisons [115]. Phenoxy herbicides have been implicated concerning, but not definitively associated with, an increased risk of non-Hodgkin lymphoma amongst agricultural workers [116]. Any such risk may be attributable to the phenoxy compounds specifically rather than being attributable to contaminating TCDD [117]. Going beyond occupational exposures, pesticides are implicated in the etiology of childhood leukaemia [118]. Pesticides have been studied concerning the regional distribu-

tions of breast cancer [119,120] based on xenoestrogen activity and related mechanisms rather than breast cancer being observed following occupational exposure to pesticides [121]. Such diverse observations concerning pesticides may be inevitable when many different chemicals are addressed under this single heading. The complexity may also be indicative of risks that can be distinguished from those mediated by recognized carcinogens.

The challenge to distinguish between multiple related agents, a corresponding multiplicity of implicated target organs and differing contexts of exposure, as outlined above for pesticides, applies equally to solvents [122], polychlorinated biphenyls [6], TCDD/dioxins [123] and perhaps other classes of agents specified in Tables 3 and 4. For solvents specifically, increased risk of lung cancer may be associated with general occupational exposure exemplified by work as a painter [124], while solvent exposure in dry cleaning work is associated with multiple tumour types not particularly including lung cancer [125]. Environmentally, solvent contaminated groundwater is a public health concern, though carcinogenesis in this context may not have been demonstrated [126]. When workplace exposures provide equivocal data concerning cancer causation, demonstration of increased risk consequent upon environmental exposure to the relevant agent(s) is particularly difficult.

Consideration of target organ becomes challenging when immediately relevant epidemiological studies are “negative”. In reference to such situations, an *unknown carcinogenic outcome* (Table 5) is not a default allocation for any situation concerning which there have been epidemiological studies which failed to demonstrate an increase in risk. Arguably, living near a properly operating nuclear reactor [127] or drinking water containing asbestos [128] are situations reasonably identified with negative studies. These situations are not included in Table 5. Both are excluded from δ -band risk because each involves a recognized carcinogen. Being recognized carcinogens, target organs specified in the albeit negative studies were target organs known from other exposure situations. For the artificial sweetener aspartame, for example, hematopoietic cancers may be inferred from animal data while brain cancers may be implicated by mechanistic considerations [129].

For agents having inadequate evidence of carcinogenicity, and hence identified in the context of situations allocated to δ -band risk (*unknown carcinogenic outcome*), target organs are not established. In many instances, however, the design of relevant studies indicates consensus between investigators as to likely target organ. Evidence upon which an inference of carcinogenicity, and hence of target organ to some extent, is made, is diverse. For situations allocated to the ϵ -band (*unlikely carcinogenic outcome*) relevant studies often identify a generally agreed target organ (Table 6).

8. Implications and consequences

8.1. An unlimited number of situations

Reference to ‘examples’ in the headings of Tables 2–6 is deliberate; none of these Tables provides a definitive listing of

relevant situations. Indeed, the degree to which situations may be further specified is readily apparent. Use of generic terms, such as pesticides, xenoestrogens and solvents, implicitly gives rise to multiple situations, each referring to a specific pesticide, xenoestrogen or solvent, etc. As examples, situations referring to DDT, atrazine and bisphenol A have been included, but many others could be specified. Reference to a chemical class indicates that individual class members may be cited in that context. Exposure to polycyclic aromatic hydrocarbons can be further evaluated with reference to particular members of that family [130] and the same applies to congeners of polychlorinated biphenyls [131] and other classes of chemicals. In theory at least, terms used to identify circumstances of exposure can be sub-divided. Agricultural work may be sub-divided with reference to sectors of rural industry. Situations may be specified with reference to geography. The utility of more precisely describing any situation is primarily dependent on the availability of relevant data. However, the potential for such more detailed descriptions precludes any notion of a definitive listing of situations.

8.2. Evolving means of data evaluation

The procedure for qualitative risk assessment described here provides a means of characterising carcinogenic risk according to the nature of the evidence (and NOT the strength of the evidence). Situations for which the evidence is of a similar nature can be recognized (Tables 2–6), and a newly described risk situation may be characterized as similar to, or different from, other situations which are relatively well recognized. The parameters used here for qualitative risk assessment are either already in use, or directly related to those in use. To that extent, what is proposed is a further development in risk characterization, and will be subject to evolution rather than being a finished product. Although primarily described with reference to hazard identification, the parameters employed are a subset of those used in quantitative risk assessment. Further development might involve qualitative approaches to potency or dose–response if such an exercise provides insight.

As noted in Section 2.3, the procedure for qualitative risk assessment (Table 1) is markedly influenced by epidemiological findings. There is only limited discriminatory power in relation to exposures involving agents identified as carcinogenic from bioassay findings alone. In regard to such findings, other approaches to data evaluation warrant citation. Approaches to risk assessment may be based on bioassay data as recently described in relation to possible causes of breast cancer [132]. Toxicological data provide a basis for quantitative risk assessment in relation to complex exposures [133]. The consideration that epidemiological and experimental data are of separate nature obviously does not mean that final understanding should emerge from only one data source. Thus, toxicological, epidemiological and other data can be taken together to indicate likely dose–response, and hence the nature of risk posed by exposure to particular substances [41].

The IPCS Framework provides another approach to the human relevance of a carcinogenic response observed in an experimental study, namely an approach based on mode of action [26]. In this context, the latter involves consideration of a series of key events along the causal pathway to cancer, identified using a weight-of-evidence approach based on Bradford-Hill criteria. A postulated mode of action is a biologically plausible sequence of key events leading to an observed effect supported by experimental observations.

Multiple approaches for using data relevant to carcinogenic risk, and formalizing its presentation and evaluation, are available. None is of universal application, and the processes have so many elements in common that an issue of mutual exclusion does not arise. Concerning a particular matter, the outcome of any data evaluation process is wholly dependent on the quality of primary findings available.

8.3. Toward prevention

Risk assessment may be readily characterized in the progression from identifying carcinogens to preventing cancer [2,134], this particular pathway being one of a number leading to the goal of reducing the burden of malignant disease. Some relationships between risk bands (Section 3.3) and prevention are note worthy. Reducing or preventing exposure in the context of situations banded as *proven* will result in reduced cancer incidence. Data to independently establish reduced incidence after the adoption of preventive measures is rarely available, and its accrual is a low priority for reasons including technical difficulty and *a priori* status. That scenario – knowledge that cancer incidence has been reduced – is less than certain as *likely* and *inferred* risk situations are considered.

Wider consideration of preventive measures targeting carcinogen exposure indicates that certainty regarding risk is a factor, but by no means the sole determinant of preventive action [28]. It is a factor to the extent that knowledge of causation provides the opportunity for intervention and immediate action may be warranted [135]. The precautionary principle is relevant [136]. A precautionary measure to reduce exposure may be warranted when causation is far from certain [137]. Ease of regulatory control is determined by the context in which exposure occurs and not the harm being confronted: it's easier to regulate food additives [138] than tobacco [139]. Alteration of behaviour, rather than regulation, may be key to cancer prevention [30] and these two dimensions may be related [140]. In light of the parameters determining the implementation and efficacy of measures to reduce or eliminate exposure to particular carcinogens, the nature of evidence establishing risk cannot be directly correlated with the imperative to implement preventive measures.

8.4. Risk perception, risk communication and risk-reducing behaviour

Risk assessment seeks to describe, for regulators and citizens, the types of cancers, the exposure circumstances at

which people will likely develop cancers, the levels of carcinogen and the associated severity of harm. The present procedure is intended as a further means of achieving this end.

The concern properly accorded to each specific circumstance of carcinogen exposure may be self-evident to those involved in cancer control, but is far from clear to the community-at-large. Surveys conducted in America [141], Europe [142], Japan [143] and Australia [144] indicate that while tobacco smoking is recognized as the principal cause of cancer, there is trivial difference in the risk accorded to a range of factors exemplified by deliberate sun exposure, alcohol consumption, food additives and pesticides. The situations considered in this review (Tables 2–6) do not encompass all those brought to the attention of the community. In particular, no provision has been made for false or fatuous assertions. Obviously, such matters are rarely addressed in the scientific literature but rumours about asbestos in tampons [145] or phthalates or dioxins leached from plastic bottles [146] pervade the Internet. What is false or fatuous in this context cannot be equated with, or evaluated as *unlikely carcinogenic outcome*.

Perceptions about particular carcinogens are not held in isolation, but influence attitudes to other hazards. Thus, people who believe that most chemical substances cause cancer worry more about electromagnetic fields than those who don't [147]. The situation may have improved since Harvard Centre for Cancer Prevention recorded in 1996 that 'it is not uncommon to meet heavy smokers who are genuinely concerned about the possible health effects of magnetic fields' [148]. Moreover, from a recent study suggesting just on half the community agrees "It seems like almost everything causes cancer", those who perceived themselves as powerless to prevent cancer were less likely to have adopted specific preventive behaviours [149].

Goldstein describes a continuum from risk assessment, through risk communication and on to broader issues [150]. The challenge of describing quantified risk by specific words, such as low, very low, minimal and negligible, has been examined [151] and there are other options [152]. Risk communication is recognized to be a singular concern in relation to cancer [153], and breast cancer genetics has been the main focus in recent times [154]. There is, however, a clear perspective that risk communication is crucial to cancer prevention [155]. The procedure described in this paper for qualitative assessment allows a broad scope of carcinogenic risk situations to be addressed. From the perspective of risk communication, the status of a newly described risk is primarily indicated by its similarity to other relatively well-understood risks in the same band. Amongst other considerations, this may allow some supposed risks to be removed from community consciousness in an authoritative and objective manner. A means of describing vastly differing risks of cancer causation may contribute to reducing confusion and increasing community awareness of proven cancer preventive measures.

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