

1 **IPCS HARMONIZATION PROJECT DRAFT FOR PEER REVIEW**
2 **Draft prepared by IPCS Workshop, April 2005, Bradford, United Kingdom**

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5 **IPCS FRAMEWORK FOR ANALYSING THE RELEVANCE OF A CANCER**
6 **MODE OF ACTION FOR HUMANS**

10 **INTRODUCTION**

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12 1. The process of cancer risk assessment has evolved over the last three decades.
13 Fundamental to this evolution has been our increasing understanding of the biology of
14 cancer and key events that distinguish the cancer process. Through the mid-1980s,
15 national and international assessments of human cancer hazard and risk depended
16 primarily on lifetime bioassays of potentially carcinogenic agents in laboratory
17 animals. Few agents had sufficient human evidence upon which to base cancer
18 assessments. Inherent in these animal-based assessments were the assumptions that
19 the observation of tumours in animals was relevant to the risk of cancer in humans,
20 and that responses observed at high doses in animals could be extrapolated
21 meaningfully, through mathematical models, to doses of regulatory relevance for
22 humans. These assumptions, while valid for many chemicals, were based primarily on
23 correlative analysis. It has become increasingly apparent that an appreciable number
24 of chemicals cause cancer in animals by a process that does not involve direct
25 interaction with DNA. These non-genotoxic carcinogens often act indirectly, for
26 example by causing persistent cellular damage leading to regenerative hyperplasia.
27 As progress has been made in the last twenty years in our understanding of the mode
28 of action (MOA) of carcinogenesis in both animals and in humans, risk assessment
29 has benefited from the use of more data on the pharmacokinetics and
30 pharmacodynamics of agents to determine the appropriateness of such assumptions
31 and to characterize the biological basis underlying the use of such assumptions. The

1 biological processes involved in some cancer MOAs are such that they are not
2 relevant to humans, for example when a critical target such as alpha 2_U-globulin,
3 present in male rats, is absent in humans.

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5 2. The postulated MOA is a biologically plausible hypothesis/basis for the sequence of
6 events leading to an observed effect supported by robust experimental observations
7 and mechanistic data. It identifies “key” cellular and biochemical events – i.e., those
8 that are both measurable and critical to the observed effect as hypothesized in the
9 postulated mode of action. Assessment of the weight of evidence for a hypothesized
10 mode of action in animals and its relevance to humans is based on consideration of
11 factors such as consistency and dose response for key events. Mode of action
12 contrasts with mechanism of action, which generally implies a detailed description
13 and sufficient understanding of the molecular basis for an effect so as to establish
14 causation in molecular terms.

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16 3. The IPCS Framework presented in this document is an analytical tool, to provide a
17 means of evaluating systematically the data available on a specific carcinogenic
18 response to a chemical in a transparent manner. Whilst it is envisaged that the
19 framework will be of value to risk assessors, both within and outside of regulatory
20 agencies, it will also be a valuable tool to the research community. Amongst reasons
21 for using the framework are:

22

- 23 • To provide a harmonized generic approach to the analysis of data.
- 24 • To ensure transparency of the consideration of use of available data and
25 reasons for the conclusions drawn.
- 26 • To provide guidance in the presentation of data.
- 27 • To identify data deficiencies and needs.
- 28 • To inform the quantitative assessment of carcinogenic risk to humans.
- 29 • To explore “what-if” scenarios, such as the impact of an equivocal event
30 (e.g. weak genotoxicity) or whether a questionable tumour response would
31 have any human relevance even if it were real.

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4. Amongst the strengths of the framework are its flexibility, general applicability to carcinogens acting by any mechanism and the ability to explore the impact of each key event on the carcinogenic response. This includes determination of the nature of the dose-response curve, the identification and location of thresholds for individual key events and their consequences for the overall tumour response curve. In addition, by considering the kinetic and dynamic factors involved in each key event, it may be possible to reach conclusions regarding the relevance or not of the carcinogenic response to specific sub-populations, for example in early life, in those with particular diseases or in those with specific polymorphisms. Alternatively, the framework can provide quantitative information on the differences between such groups. Application of the framework can also more generally inform in risk characterization of the chemical, even when it is concluded that the carcinogenic response per se is not relevant to humans.

5. As stated at the outset, MOA analysis and its human relevance counterpart are aspects of the hazard identification and characterization phases of risk assessment (NAS, 1983; Meek et al, 2003 (Appendix). Consistent with this paradigm, the human relevance case studies referred to in this report contribute to, but do not complete, a risk assessment for the chemicals under study. This is because a complete risk characterization requires analysis of human exposure in the “real world” of daily and lifetime activities, whereas hazard identification and characterization consider effects, only. This critical distinction is often overlooked or ignored.

6. Hazard characterization – and related MOA analysis – focuses on dose-response relationships established in laboratory or epidemiological studies that identify toxic effects. Risk characterization seeks to describe the relationship between these effects and the dose(s) to which humans are exposed in order to understand and estimate the nature and likelihood of effects in humans who are generally exposed at lower dose levels.

1 7. Estimating these generally lower human exposure levels is the task of the exposure
2 analysis component of the risk assessment process. This usually involves extensive
3 analysis of data collected from environmental media, and plant and animal tissues, as
4 well as that derived from pharmacokinetic models. This process depends also on real
5 world analysis of human activity patterns and life style factors that may bring about
6 exposure. Ideally, based on this information, a range of exposure scenarios is
7 developed for different groups (men, women, children, infants, special groups, based
8 for example on ethnicity or occupation) for use in identifying populations of concern.
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11 **THE ROLE OF THE INTERNATIONAL PROGRAMME ON CHEMICAL**
12 **SAFETY IN DEVELOPING THE FRAMEWORK FOR ANALYSING THE**
13 **RELEVANCE OF A CANCER MODE OF ACTION FOR HUMANS**
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15 8. The International Programme on Chemical Safety (IPCS) has been leading an effort
16 to harmonize approaches to cancer risk assessment as part of its larger project on the
17 *Harmonization of Approaches to the Assessment of Risk from Exposure to Chemicals*.
18 As described in Sonich-Mullin et al. (2001), a major impediment to harmonization
19 identified in the consideration of weight-of-evidence was the evaluation of MOA in
20 animals. Sonich-Mullin et al. (2001) provided a framework for evaluating MOA of
21 chemical carcinogenesis in animals and recognized the importance of moving on to
22 the next step in the overall characterization of cancer hazard and risk in humans: the
23 assessment of relevance of the MOA of animal carcinogenesis to humans. Adoption
24 of the MOA framework concept is proceeding through its incorporation in the revised
25 U.S. EPA Risk Assessment Guidelines for Carcinogens (U.S. EPA, 1999, 2005), and
26 is now commonly used by other regulatory agencies and international organizations.
27 In the United Kingdom (UK), the framework is being used for the assessment of
28 pesticides and industrial chemicals. The UK Committee on Carcinogenicity has
29 noted its value with regard to both harmonization between agencies and internal
30 consistency in its latest Guidelines (COC, 2004). It has also been adopted and is
31 being used by agencies in Australia and in Canada, in the evaluation of Existing

1 Chemicals under the Canadian Environmental Protection Act. The European Union
2 has incorporated the framework into the technical guidance documents that are being
3 updated on evaluating new and existing industrial chemicals and biocides, including
4 carcinogenicity. With regard to international organizations, of particular note is the
5 use of the framework by the WHO/FAO Joint Meeting on Pesticide Residues (JMPR)
6 in its evaluation of pyrethrin extract and its incorporation into the resulting
7 monograph. *[Peer reviewers are invited to provide further examples].*

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9 9. The step to extend this concept to human relevance is being taken forward by IPCS in
10 cooperation with international partners. It was the subject of an IPCS international
11 workshop convened in Bradford, United Kingdom, from 21-23 April 2005. This
12 workshop prepared draft text for a unified IPCS Framework, including updating the
13 2001 Mode of Action Framework. The framework text, and the steps leading to its
14 development are discussed in detail in the following sections.

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16

17 **THE 2001 IPCS CONCEPTUAL MOA FRAMEWORK FOR CANCER RISK** 18 **ASSESSMENT**

19

20 **Purpose of the Framework**

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22 10. The IPCS Mode of Action Framework remains a fundamental basis for the unified
23 IPCS Framework for Analysing the Relevance of a Cancer Mode of Action for
24 Humans. The framework provides a generic approach to the principles commonly
25 used when evaluating a postulated MOA for tumour induction in animals by a
26 chemical carcinogen. Thus, the framework is a tool that provides a structured
27 approach to the assessment of the overall weight of the evidence for the postulated
28 MOA. It outlines the thought processes involved in making use of mechanistic data in
29 risk assessment in a structured way. In this context, a supported MOA would have
30 evidence provided by robust mechanistic data to establish a biologically plausible
31 explanation.

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2 11. The framework is designed to bring transparency to the analysis of a postulated MOA
3 and, thereby, promote confidence in the conclusions reached through the use of a
4 defined procedure which mandates clear and consistent documentation of the facts
5 and reasoning including inconsistencies and uncertainties in the available data. The
6 animal MOA framework analysis is the first step in the hazard characterization
7 process and can be greatly aided by the presentation of tabular summaries of
8 comparative data on incidence of intermediate endpoints and tumours. It is also
9 envisaged that the framework will be useful to both regulators and researchers in
10 identifying research needs based on clear delineation of data gaps and inconsistencies.

11

12 12. The animal MOA framework is not a checklist of criteria, but rather an analytical
13 approach. The purpose of the framework is to provide a systematic means of
14 considering the weight of the evidence for a MOA in a given situation; it is not
15 designed to give an absolute answer on sufficiency of the information as this will vary
16 depending on the circumstance. It is envisaged that the animal MOA framework will
17 be helpful in performing risk assessments of chemical carcinogens across all sectors
18 (drugs, industrial chemicals, pesticides, food additives, etc.). In the resulting risk
19 assessment documentation, the framework analysis could be appropriately positioned
20 within the hazard characterization section. It may be regarded as an essential
21 precursor to any discussion of human relevance, dose-response relationships and risk
22 characterization. The framework may also find use as a stand-alone analytical tool,
23 and it is, therefore, important that the relevant studies on which the conclusions are
24 based be fully referenced in the text of the framework analysis.

25

26 13. A mode of action, comprising the same set of key events, may apply to many
27 different compounds. The evidence necessary to establish that a specific mode of
28 action is responsible for a given carcinogenic response will be substantial the first
29 time such a mode of action is proposed. As subsequent compounds are found to share
30 this mode of action, the “barrier” to acceptance will be become lower, though it will

1 always be necessary to establish rigorously that the key events comprising the mode
2 of action occur, and that they fulfil the criteria indicated below.

3
4 14. Expert judgment and peer review are essential elements for a given mode of action to
5 be accepted as responsible for a carcinogenic response. Acceptance does not
6 necessarily mean unanimity, but a majority of the scientists reviewing the MOA
7 should agree that the relevant scientific information has been identified and
8 appropriately analysed, that the “key events” have been identified and are supported
9 by the information presented, that their relationship to carcinogenesis has been clearly
10 established in the hypothesized MOA and that alternate MOAs have been considered
11 and rejected. It is important to emphasize that review of a MOA concerns its key
12 elements and does not need to be tissue-specific. Thus, a MOA that has previously
13 been peer reviewed and accepted for one tissue and which is applicable to other
14 tissues does not need to be subjected to the scientific review and acceptance process.
15 For example, cytotoxicity and consequent regeneration is a well-known and well-
16 documented mode of action for a wide variety of chemicals that affect different
17 tissues.

18
19 15. Scientific peer participation is a prerequisite to acceptance of a postulated mode of
20 action. Peer participation includes both peer involvement and peer review. Peer
21 involvement implies that the hypothesized MOA is the product of the collective
22 efforts of a number of scientists who have identified, reviewed and analysed data and
23 formulated the MOA hypothesis. Peer review implies that the proposed MOA has
24 been critically reviewed by scientists independent of the process of development of
25 the MOA. In many cases, this peer review may include publication in the scientific
26 literature, allowing for widespread review and comment. Presentations and discussion
27 at scientific meetings and workshops also constitute peer involvement that contributes
28 to acceptance by the scientific community.

29
30 16. As knowledge advances, the characterization of a MOA will change. Additional key
31 events may be identified, and others may be refined or even dropped. Nevertheless,

1 significant changes to the key events also need some general acceptance, through peer
2 review, such as described above.

3

4 17. It is important that a compendium of agreed modes of action be constructed and
5 maintained in a publicly accessible location. Ideally this should be a website. This
6 would comprise a series of MOAs and their associated key events, for reference by
7 those developing framework analyses for compounds which may act by similar
8 modes of action.

9

10 18. To assist in the dissemination and application of the unified IPCS Framework a
11 database of informative cases should be constructed and maintained. These would
12 comprise worked examples that have been analysed using the framework, to provide
13 an indication of the relevant level of detail of the analyses and nature of the weight of
14 evidence required to support acceptance of a proposed MOA in causing the
15 carcinogenic response. Such cases would be particularly valuable early in the
16 development of a new MOA.

17

18 19. Some mechanism will need to be established to judge the stage of acceptability of
19 proposed modes of action and modifications to existing modes of actions, perhaps
20 through a series of international workshops.

21 **Framework Guidelines: Proposed Section Headings**

22

23 20. In development of the unified IPCS Framework, the 2001 MOA Framework text has
24 been updated and this revised version is presented below.

25 ***1. Introduction***

26 21. This section describes the cancer endpoint or endpoints that have been observed and
27 identifies which of these is addressed in the analysis. The nature of the framework is
28 such that only one mode of action is analysed at a time; hence, for example, tumour
29 types associated with a different mode of action, even if recorded in the same
30 animals, will require separate framework analyses. However, where different tumours

1 are induced by the same (or a very similar) mode of action, they are best addressed in
2 a single analysis.

3 ***2. Postulated mode of action (theory of the case)***

4 22. This section comprises a brief description of the sequence of events on the path to
5 cancer for the postulated mode of action of the test substance. This explanation of the
6 sequence of events leads into the next section which identifies the events considered
7 “key” (*i.e.* necessary and measurable) given the data base available for the analysis.

8 ***3. Key events***

9 23. This section briefly describes the “key events” — *i.e.* measurable events that are
10 critical to the induction of tumours as hypothesized in the postulated mode of action.
11 To support an association, a body of experiments needs to define and measure an
12 event consistently. Pertinent observations, *e.g.* tumour response and key events in
13 same cell type, sites of action logically relate to event(s), increased cell growth,
14 specific biochemical events, changes in organ weight and/or, histology, proliferation,
15 perturbations in hormones or other signalling systems, receptor-ligand changes,
16 effects on DNA or chromosomes, and impact on cell cycles.. For example, key events
17 for tumours hypothesized to be associated with prolonged regenerative proliferation
18 might be cytotoxicity as measured histopathologically and an increase in labelling
19 index. As another example, key events for induction of urinary bladder tumours
20 hypothesized to be due to formation of bladder stones composed primarily of calcium
21 phosphate might include elevated urinary calcium, phosphate and pH and formation
22 of bladder stones followed by irritation and regenerative hyperplasia of the
23 urothelium.

24 ***4. Dose–response relationship***

25 24. This section should characterize the dose–effect/response relationships for each of the
26 key events and for the tumour response, and discuss their inter-relationships , with
27 particular reference to the shape of the dose-effect/response curves and to any
28 thresholds. Ideally, one should be able to correlate the dose-dependency of the
29 increases in incidence of a key event with increases in incidence or severity (*e.g.*

1 lesion progression) of other key events occurring later in the process, and with the
2 ultimate tumour incidence. Comparative tabular presentation of incidence of key
3 events and tumours is often helpful in examining dose–response.

4 25. The biological plausibility of any postulated mode of action in humans depends on a
5 consideration of dose-effect and dose-response relationships. If a high experimental
6 dose of a given compound is needed to result in an obligatory step in a mode of
7 action, then the relevance to human risk becomes a matter of exposure. Thus, the
8 exposure assessment step of the subsequent risk characterization is critical to the
9 proper evaluation of human cancer potential.

10 26. It is important to consider whether there are fundamental differences in the biological
11 response (i.e., dose transitions) at different parts of the dose response curve for
12 tumour formation (Slikker et al, 2004). If so, key events relevant to the different parts
13 of the dose-response curve will need to be defined and used in the framework
14 analysis.

15 ***5. Temporal association***

16 27. This section should characterize the temporal relationships for each of the key events
17 and for the tumour response. The temporal sequence of key events leading to the
18 tumour response should be determined. Key events should be apparent before
19 tumour appearance and should be consistent temporally with each other; this is
20 essential in deciding whether the data support the postulated mode of action.
21 Observations of key events at the same time as the tumours (*e.g.* at the end of a
22 bioassay) do not contribute to considerations of temporal association, but can
23 contribute to analysis in the next section. Most often, complete data sets to address
24 the criterion of temporality are not available.

25 ***6. Strength, consistency and specificity of association of tumour response with key*** 26 ***events***

27 28. This section should discuss the weight of evidence linking the key events, precursor
28 lesions and the tumour response. Stop/recovery studies showing absence or reduction
29 of subsequent events or tumour when a key event is blocked or diminished are

1 particularly important tests of the association. Consistent observations in a number of
2 such studies with differing experimental designs, increases that support since different
3 designs may reduce unknown biases or confounding. Consistency, which addresses
4 repeatability of key events in the postulated mode of action for cancer in different
5 studies is distinguished from coherence, however, which addresses relation of the
6 postulated mode of action with observations in the broader database (see point 7).
7 Pertinent observations are, *e.g.*, tumour response and key events in same cell type,
8 sites of action logically related to event(s), initiation–promotion studies, and
9 stop/recovery studies.

10 **7. Biological plausibility and coherence**

11 29. The postulated mode of action and the events that are part of it need to be based on
12 current understanding of the biology of cancer to be accepted, though the extent to
13 which biological plausibility as a criterion against which weight of evidence is
14 assessed is necessarily limited, due to considerable gaps in our knowledge in this
15 regard. One should consider whether the mode of action is consistent with what is
16 known about carcinogenesis in general (biological plausibility) and in relation to what
17 is also known for the substance specifically (coherence). For the latter, likeness of the
18 case to that for structural analogues may be informative (*i.e.* structure–activity
19 analysis). Information from other compounds that share the postulated MOA may be
20 of value, such as sex, species and strain differences in sensitivity and their
21 relationship to key events. Additionally, this section should consider whether the
22 database on the agent is internally consistent in supporting the purported mode of
23 action, including that for relevant non-cancer toxicities. Some modes of action can be
24 anticipated to evoke effects other than cancer, *e.g.* reproductive effects of certain
25 hormonal disturbances that are carcinogenic. Moreover, some modes of action are
26 consistent with an observed lack of genotoxicity. Coherence, which addresses relation
27 of the postulated mode of action with observations in the broader database — for
28 example, association of mode of action for tumours with that for other endpoints —
29 needs to be distinguished from consistency (addressed in Point 6 above) which

1 addresses repeatability of key events in the postulated mode of action for cancer in
2 different studies.

3 **8. Other modes of action**

4 30. This section discusses alternative modes of action that logically present themselves in
5 the case. If alternative modes of action are supported, they need their own framework
6 analysis. These should be distinguished from additional components of a single mode
7 of action which likely contribute to the observed effect, since these would be
8 addressed in the analysis of the principal mode of action.

9 **9. Uncertainties, Inconsistencies, and Data Gaps**

10 31. Uncertainties should include those related to both the biology of tumour development
11 and those for the database on the compound of interest. Inconsistencies should be
12 flagged and data gaps identified. For the identified data gaps, there should be some
13 indication of whether they are critical as support for the postulated mode of action or
14 simply serve to increase confidence therein.

15 **10. Assessment of postulated mode of action**

16 32. This section should include a clear statement of the outcome with an indication of the
17 level of confidence in the postulated mode of action — *e.g.* high, moderate or low.
18 Consideration needs to be given as to whether any identified MOA is the same as that
19 proposed for other compounds. If so, the extent to which the key events fit this MOA
20 needs to be stated explicitly. Any major difference should be noted, and their
21 implications for the MOA discussed. If a novel MOA is being proposed this should
22 be clearly indicated.

23

24 **ADDRESSING THE ISSUE OF HUMAN RELEVANCE**

25

26 33. In 2000, an IPCS Harmonization Project Cancer Planning Work Group¹ convened in
27 Carshalton, United Kingdom (IPCS, 2000). Among the recommendations of that

¹ This initial IPCS Working Group differed in membership from the subsequent IPCS working group convened to work on the human relevance project.

1 meeting was the suggestion that IPCS and ILSI move forward together and in parallel
2 on the development of the extension of the IPCS MOA Framework toward addressing
3 human relevance. It was recognized that ILSI could provide much help in technical
4 workshops. In June 2001, the International Life Sciences Institute Risk Science
5 Institute (ILSI/RSI) with support from the US EPA and Health Canada formed a
6 working group to examine key issues in the use of mode of action information to
7 determine the relevance of animal tumours. These efforts have resulted in several
8 published reports that are described below. An IPCS Cancer Working Group,
9 convened on 3-5 March 2004 in Arlington, Virginia, USA agreed that that these
10 reports should form the starting point for further exploration of the issue of human
11 relevance of animal tumours by IPCS with the goal of developing a unified IPCS
12 framework for use of MOA information in risk assessment for regulatory and other
13 purposes (IPCS, 2004).

14
15 34. To address the issue of the human relevance of the MOA(s) determined in animals,
16 ILSI/RSI charged its working group with expanding the IPCS MOA Framework to
17 include evaluation of the human relevance of a cancer MOA determined in animals.
18 The details of the process, the case studies, and the framework are published as a
19 series of papers in the November 2003 issue of *Critical Reviews in Toxicology*
20 (*CRTJ*) (Cohen et al., 2003; Meek et al., 2003). These articles briefly describe the
21 ILSI/RSI Human Relevance Framework (HRF) and provide a user's guide for its
22 application. In addition, references to specific examples on which the framework is
23 based are included. Several iterations of case studies of chemicals with generally
24 well-known modes of action were used to develop the integrated framework. The
25 intent was to provide guidance for a disciplined, transparent process evaluating the
26 mode of action in animals and each key event with respect to human relevance.

27
28 The ILSI/RSI HRF is based on three fundamental questions:

- 29
30 1. Is the weight of evidence sufficient to establish the mode of action (MOA) in
31 animals?

- 1 2. Are key events in the animal MOA plausible in humans?
2 3. Taking into account kinetic and dynamic factors, are key events in the animal
3 MOA plausible in humans?
4

5 35. These are followed by an explicit description of confidence in the evaluation,
6 identification of specific data gaps, and the implications for risk assessment. It was
7 emphasized by ILSI/RSI that use of this framework would form part of the hazard
8 characterization step of the overall risk assessment process.
9

10
11 **DEVELOPMENT OF A UNIFIED IPCS FRAMEWORK GUIDANCE**
12 **DOCUMENT BASED ON THE IPCS MOA FRAMEWORK AND THE ILSI/RSI**
13 **HRF**
14

15 36. The 2004 IPCS Cancer Working Group discussed the type of document that would be
16 produced as a result of its task to extend the MOA Framework to address human
17 relevance. It was recognized that one integrated guidance document (a "unified
18 framework") that worked as a whole would be needed to facilitate uptake and use by
19 regulatory and other risk assessment bodies. The guidance could be supplemented by
20 including publication of the other materials generated through the process (e.g. issues
21 papers and case studies).
22

23 37. Overall, there was general agreement among Working Group members that the
24 questions identified as the critical components of the ILSI/RSI HRF were important
25 and appropriate for addressing the issue of human relevance of a mode of action
26 determined in animals. However, several issues were identified that could benefit
27 from additional clarification, development or expansion. These issues are addressed
28 in the IPCS effort and result in modification of the ILSI/RSI HRF.
29

30 38. The unified IPCS Framework, developed by adopting the ILSI/RSI HRF and by
31 modifying it as discussed by the Cancer Working Group and at a Workshop convened

1 for this purpose in Bradford, UK, 21-23 April, 2005 (IPCS, 2005), is presented as an
2 approach to answering a series of three questions, leading to a documented, logical
3 conclusion regarding the human relevance of the MOA underlying animal tumours.
4 The application of the guidance results in a narrative with four sections that may be
5 incorporated into the hazard characterization of a risk assessment. The sections are as
6 follows (see Figure 1.):

7

- 8 1. Is the weight of evidence sufficient to establish a mode of action (MOA)
9 in animals?
- 10 2. Can human relevance of the MOA be reasonably excluded on the basis of
11 fundamental, qualitative differences in key events between experimental
12 animals and humans?
- 13 3. Can human relevance of the MOA be reasonably excluded on the basis of
14 quantitative differences in either kinetic or dynamic factors between
15 experimental animals and humans?
- 16 4. Conclusion: Statement of confidence, analysis, and implications.

17

18 39. In applying this framework for a given chemical, tumours of each animal target organ
19 observed are evaluated independently, with the assumption that different modes of
20 action are possible in different organs, though based on this analysis, modes of action
21 in different tissues may be similar. Similarly, an evaluation of the likelihood of
22 congruence between target organ(s) in different species and in humans needs to be
23 made, based on the mode of action analysis.

24

1 **Is the Weight of Evidence Sufficient to Establish a Mode of Action in Animals?**

2 40. Answering this first question in the unified IPCS Framework requires application of
3 the (updated) IPCS MOA Framework described earlier in this document. The steps in
4 the MOA Framework are:

5

- 6 A. Postulated MOA.
- 7 B. Key Events; associated critical parameters.
- 8 C. Dose Response Relationships.
- 9 D. Temporal Association.
- 10 E. Strength, Consistency and Specificity of Association of Key Events and
11 Tumour Response.
- 12 F. Biological Plausibility and Coherence.
- 13 G. Possible Alternative MOAs.
- 14 H. Uncertainties, Inconsistencies, and Data Gaps.
- 15 I. Conclusion about the MOA.

16

17 41. This process incorporates an evaluation of the weight of evidence for possible
18 alternative MOAs at a given site, and an evaluation of the overall strength of evidence
19 supporting the MOA under consideration. Ultimately, a decision concerning the
20 weight of evidence supporting the MOA and the level of confidence in that decision
21 must be made. It also identifies critically important data gaps which, when filled,
22 would increase confidence in potential modes of action. It is also necessary to
23 establish whether the postulated MOA has already been described for other
24 chemicals, in which case there will be information available on human relevance, or
25 whether the proposed MOA is novel, in which case human relevance needs to be
26 assessed *de novo*.

27

28 42. For a given chemical, the primary sources of information for evaluating a MOA are
29 often likely data generated for that specific chemical in the animal model in which
30 tumours were produced. Obviously, data from other sources can and should also be
31 used, as appropriate, along with data on chemicals with similar chemical structures,

1 the same or similar modes of action, or both. If the mode of action for a chemical is
2 novel, considerably more data will be required to support the conclusion that it is
3 related to the carcinogenic process of the tumours induced by that chemical than
4 subsequent examples of chemicals acting by the same mode of action. The ILSI/RSI
5 working group and the IPCS Bradford Workshop did not address the issue of how
6 much data is sufficient to support a specific mode of action for a given chemical,
7 except by way of example within the case studies and recognition that acceptance of a
8 MOA requires scientific consensus (see above). Consideration at this stage of the
9 mode of action in the context of potential variations between animals and humans
10 also facilitates addressing subsequent steps in the framework.

11
12 **Can human relevance of the MOA be reasonably excluded on the basis of**
13 **fundamental, qualitative differences in key events between experimental animals**
14 **and humans?**

15
16 43. The wording of this question was changed from that in the ILSI/RSI HRF, following
17 discussion at the IPCS Workshop on the implications of a Yes or a No answer to the
18 original question. In answering the original question, only an unequivocal No would
19 be sufficient to permit the conclusion that the animal MOA was not relevant to
20 humans. Also, it was recognized that translation of the word "plausible" into other
21 languages could be problematic. The question was therefore reworded to enable a
22 Yes/No answer, but qualified by the descriptor "reasonably", based on recognition
23 that decisions about the adequacy of weight of evidence are not absolute but involve
24 judgment based on transparent analysis.

25
26 44. This step represents a qualitative assessment of the relevance of the MOA to human
27 cancer potential. Listing the critical specific key events that occur in the animal mode
28 of action and directly evaluating whether each of the key events might or might not
29 occur in humans facilitates consideration and transparent presentation of the relevant
30 information. Presentation in tabular form, referred to as a concordance table, can be
31 helpful in delineating the relevant information. (for an example see Meek et al, 2003;

1 Case Study 6: kidney and liver tumours associated with chloroform exposure, Table
2 7, p. 630) The key events (and possibly some of the critical associated processes) are
3 listed with the information regarding these events for the animals in which the tumour
4 was observed. It is intended that the information in these tables be brief, since a
5 narrative explanation is expected to accompany the table. In the right-hand column,
6 the effect on humans for each of the key events is evaluated. An additional column
7 for the results in a different strain, species, sex, or route of administration that does
8 not result in tumours can be useful if information is available for comparison to the
9 model that leads to tumours. In addition, factors may be identified that, whilst not key
10 themselves, can modulate key events and so contribute to differences between
11 species. Such factors include genetic differences in pathways of metabolism,
12 competing pathways of metabolism, cell proliferation induced by concurrent
13 pathology. Any such factors identified should be noted in a footnote to the
14 concordance table.

15
16 45. The evaluation of the concordance for a given chemical in humans is an evaluation of
17 the MOA in humans, rather than an evaluation of the specific chemical. In general,
18 the initial key events are likely more chemical-specific, for example the induction
19 response by phenobarbital in rodent liver, or the formation of a cytotoxic metabolite
20 from chloroform by CYP2E1. Later events would be more generic to the MOA, for
21 example pleiotropic stimulation of hepatic proliferation or regenerative hyperplasia.
22 Information that can be utilized to evaluate the key events in humans can come from
23 *in vitro* and *in vivo* studies on the substance itself, but also can involve basic
24 information regarding anatomy, physiology, genetic disorders, epidemiology, and any
25 other information that is known regarding the key events in humans. Information
26 concerning an evaluation of the key event in humans exposed directly to the specific
27 chemical is almost always unavailable.

28
29 46. In evaluating the concordance of the information in humans to that in animals, a
30 narrative describing the weight of evidence and an evaluation of the level of

1 confidence for the human information needs to be provided. Some specific types of
2 information that are useful include the following:

3
4 1. Cancer incidences at the anatomical site and cell type of interest, including age,
5 sex, ethnic differences and risk factors, including chemicals and other
6 environmental agents.

7
8 2. Knowledge of the nature and function of the target site including development,
9 structure (gross and histologic), and control mechanisms at the physiological,
10 cellular, and biochemical levels.

11
12 3. Human and animal disease states that provide insight concerning target organ
13 regulation and responsiveness.

14
15 4. Human and animal responses to the chemical under review or analogs following
16 short, intermediate, or long-term exposure, including target organs and effects.

17
18 47. Obviously, a substantial amount of information is required to conclude that the given
19 mode of action is not relevant to humans. If such a conclusion is strongly supported
20 by the data, then chemicals producing animal tumours only by that mode of action
21 would not pose a cancer hazard to humans and no additional risk characterization for
22 this endpoint is required. Since there is no cancer hazard, there is no cancer risk for
23 the tumour under consideration.

24
25 48. The question of relevance considers all groups and life-stages. It is possible that the
26 conditions under which a mode of action operates occur primarily in a susceptible
27 sub-population or life-stage, for example, in those with a pre-existing viral infection,
28 hormonal imbalance, or disease state. Special attention is paid to whether tumours
29 could arise from early-life exposure, considering various kinetic and dynamic aspects
30 of development during these life-stages. Any information suggesting quantitative
31 differences in susceptibility is identified for use in risk characterization.

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Can human relevance of the MOA be reasonably excluded on the basis of quantitative differences in either kinetic or dynamic factors between experimental animals and humans?

49. The wording of this question was changed from that in the ILSI/RSI HRF, following discussion at the IPCS Workshop on the implications of a Yes or a No answer to the original question. In answering the original question, only an unequivocal No would be sufficient to permit the conclusion that the animal MOA was not relevant to humans. The question was therefore reworded to enable a Yes/No answer, but qualified by the descriptor “reasonably”, based on recognition that decisions about the adequacy of weight of evidence are not absolute but involve judgment based on transparent analysis.

50. For purposes of human relevance analysis, if the experimental animal MOA is judged to be qualitatively relevant to humans, a more quantitative assessment is required that takes into account any kinetic and dynamic information that is available from both the experimental animals and humans. Such data will of necessity be both chemical and MOA specific and will include the biologically effective doses required to produce the relevant kinetic and dynamic responses from which neoplasia can arise. Kinetic considerations include the nature and time course of chemical uptake, distribution, metabolism and excretion, while dynamic considerations include the consequences of the interaction of the chemical with cells, tissues and organs. On occasion, the biologically effective dose that would be required to create these conditions would not be possible in humans. It may also be that quantitative differences in a biological process involved in a key event, for example the clearance of a hormone, are so great that the animal MOA is not relevant to humans. However, the IPCS Workshop recognised that only in rare instances is it likely that it will be possible to dismiss human relevance on the basis of quantitative differences. As with the qualitative assessment, a tabular comparison of quantitative data from the experimental animals and humans can facilitate the evaluation (for example, see Meek et al, 2003; Case

1 study 5, thyroid tumors associated with exposure to Phenobarbital, Table 6, p. 624).
2 Useful comparisons can also be made with key events identified from studies of other
3 compounds believed to induce effects by a similar MOA.
4

5 **Statement of Confidence, Analysis, and Implications**

6

7 51. Following the overall assessment of each of the three questions, a statement of
8 confidence is necessary that addresses the quality and quantity of data underlying the
9 analysis, consistency of the analysis within the framework, consistency of the
10 database, and the nature and extent of the concordance analysis. An evaluation of
11 alternative modes of action, using comparable analyses and rigor, is also essential. A
12 critically important outcome of adequate consideration of the weight of the evidence
13 for an overall mode of action and the qualitative and quantitative concordance is the
14 identification of specific data gaps that can be addressed experimentally in future
15 investigations to increase confidence.
16

17 52. In rare circumstances, there may be conclusive epidemiological data on the cancer
18 risk from a chemical that shares the MOA of the compound under consideration, i.e.
19 the compound does or does not cause cancer in humans. Obviously, such data would
20 lend considerable weight to the conclusion of the human relevance evaluation.
21 However, there may be occasions when, despite it being possible to establish an
22 MOA in animals, there is insufficient information on the key events in humans to
23 reach a clear conclusion on human relevance. In such circumstances it might be
24 possible to bridge this data gap by using epidemiological data. For example, the
25 database on key events in humans for compounds that act like phenobarbital to induce
26 hepatic tumours is incomplete. However, there are robust epidemiological data
27 showing that exposure to phenobarbital for prolonged periods at relatively high doses
28 does not cause cancer in humans. One possibility therefore, is to “read across” from
29 these findings with phenobarbital to any other compound that shares its MOA in
30 animals in inducing rodent liver tumours and to conclude that the tumours caused by
31 such a compound are not relevant to the risk assessment of the compound in humans.

1 Such a conclusion would be critically dependent on the reliability of the
2 epidemiological data and the similarity between the MOA for the chemical under test
3 to that of the compound for which there are epidemiological data available.
4

5 53. In applying the framework to case studies, it is apparent that much current research
6 does not address key questions that would facilitate an analysis of an animal MOA or
7 its relevance to humans. Often this has been because of lack of transparent delineation
8 of key data gaps based on consideration of the data in analytical frameworks such as
9 that presented here.
10

11 54. Also, the output of formal human relevance analysis is not restricted to determination
12 of whether or not an endpoint in animals is relevant to humans. Rather, consideration
13 of the relevant information in a transparent, analytical framework provides much
14 additional information which is critically important in subsequent steps in the risk
15 characterization for relevant effects. Based on a human relevance analysis for a
16 proposed mode of action for relevant effects, it may be possible to predict, for
17 example, site concordance or not of observed tumours in animals to humans.
18 Analysis often also provides indication of those components of a proposed mode of
19 action which may only operate over a certain dose range. This needs to be noted and
20 addressed subsequently in risk characterization. It also often provides information on
21 relevant modulating factors which are likely to affect risk.
22

23 55. Importantly, it also contributes to identification of any special sub-populations (e.g.,
24 those with genetic predisposition) who are at increased risk and often provides
25 information relevant to consideration of relative risk at various life stages. In some
26 cases, this may not be based on chemical-specific information but rather inference,
27 based on knowledge of the mode of action as to whether or not specific age groups
28 may be at increased or decreased risk.
29

30 56. The data and their analysis using the framework should be reported in a transparent
31 manner, enabling others to determine the basis of the conclusions reached with

1 respect to the key events, the exclusion of other MOAs and the analysis of human
2 relevance. As the specific form of presentation will vary with the type of data
3 available, it is not helpful to be prescriptive on how the information should be
4 reported. However, presentation should include sufficient details on the context and
5 thought processes to ensure transparency of the conclusions reached. The use of
6 appropriate tables can be helpful in presenting certain data such as comparative
7 analysis of key events in experimental animals and humans.

8

9 **Application of the IPCS Framework to DNA-reactive carcinogens**

10

11 57. Because of similarities in the carcinogenic process between rodents and humans and
12 the comparable initial interactions with DNA by DNA-reactive carcinogens, it would
13 be expected that, in general, DNA-reactive carcinogens would be assessed as
14 progressing to the step of “YES, the key events in the animal MOA could occur in
15 humans” in the ILSI/RSI HRF as was the case for ethylene oxide (Meek et al., 2003)
16 and "NO", to the equivalent step in the IPCS Framework which asks the question "can
17 human relevance of the MOA be reasonably excluded on the basis of fundamental
18 qualitative differences in key events between animals and humans". In a recent paper,
19 Preston and Williams (2005, in press) presented a set of key events for tumour
20 development that provided a guide for the use of the ILSI/RSI HRF with DNA-
21 reactive carcinogens. This guide supported the view that for most DNA-reactive
22 chemicals, the animal MOA would be predicted to occur in humans. However, it was
23 also argued that there could be exceptions and that the ILSI/RSI HRF would be a
24 valuable tool for identifying these. The ILSI/RSI HRF and the IPCS Framework can
25 also assist in quantifying differences in key events between rodents and humans that
26 may be of value in extrapolating risk to humans. Not all rodent DNA-reactive
27 carcinogens have been established to be human carcinogens as judged by the IARC
28 review process. For some of these exceptions, this human-rodent difference in tumour
29 response is attributable to lower exposure of humans to the agent or to the relative
30 insensitivity of epidemiological studies to detect tumour responses at low exposure
31 levels. However, there are other reasons for such differences that are based on

1 biological considerations. For example, if a DNA-reactive carcinogen induces
2 tumours *only* in a species-specific organ (e.g., Zymbal gland in rodents), it is possible
3 that the animal MOA based on key events might not occur in humans, though
4 available data on mode of action would need to be considered to permit such a
5 conclusion.. Similarly, the generally more proficient DNA repair processes that occur
6 in humans than in rodents or a unique pathway of bioactivation in rodents could result
7 in there being “YES” answers to the steps in the IPCS Framework that address the
8 queries “ Can human relevance of the MOA be reasonably excluded on the basis of
9 fundamental qualitative differences in key events between animals and humans ?”
10 and/or “Can human relevance of the MOA be reasonably excluded on the basis of
11 quantitative differences in either kinetic or dynamic factors between animals and
12 humans?”. Alternatively, the IPCS Framework could provide quantitative
13 information on these processes for use later in the risk characterization step.
14

15 58. The need in order to apply the IPCS Framework for DNA-reactive carcinogens is to
16 develop a set of key events that would clearly describe the cancer process and use
17 these as the guide for establishing the human relevance of a rodent tumour MOA for
18 any particular DNA-reactive carcinogen under consideration
19
20

21 **CONCLUSIONS**

22

23 59. As additional data relevant to identification of potential MOAs are obtained, it is
24 becoming increasingly clear that there often are biological linkages among different
25 types of toxic effects. In some cases, a MOA will lead to organ toxicity that in turn is
26 a key event in the carcinogenic pathway for that organ. In other cases, a MOA may
27 lead to toxic effects in multiple organs. In still other cases, a MOA may lead to
28 different toxic effects at different life stages. Where appropriate the weight of
29 evidence for an hypothesized MOA for these effects should be analysed in a
30 consistent fashion. Application of the Framework would be an invaluable tool for
31 harmonization across endpoints.

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1. A unified IPCS Framework, based on the work by IPCS on a MOA framework and by ILSI RSI on a human cancer relevance framework has been developed.
2. Many aspects of the original frameworks have been adopted but a number of changes have been made to improve clarity and to introduce some elements not previously considered (e.g. sensitive sub-populations), based on experience gained in their application from the time since their publication.
3. The utility of the framework as an analytical tool within the overall risk assessment paradigm, i.e. in hazard characterization has been emphasized, and the role of exposure assessment in risk characterization has been clarified.
4. Prior to embarking on a framework analysis, there needs to be careful evaluation of the weight of evidence for a carcinogenic response in experimental animals.
5. Attention is drawn specifically to the need to consider potentially susceptible sub-groups, for example in different life stages or those with certain disease states.
6. The importance of considering dose-effect and changes in effect at different parts of the dose-response curve leading to different key events for the MOAs at different doses has been emphasized.
7. The need to separate key events from modulating factors and to consider their potential quantitative impact in the risk characterization was emphasized.
8. The framework is applicable to all carcinogens, whatever the MOA. Some guidance is provided on developing MOAs for compounds that are DNA reactive.
9. The process whereby a MOA is accepted is described.

- 1 10. It is recommended that a compendium of MOAs with agreed key events be
2 established and maintained.
3
- 4 11. It is recommended that a database of cases where the framework has been
5 utilized, particularly when early in the development of a MOA, should be
6 compiled and maintained.
7
- 8 12. It is concluded that the framework is of value to both risk assessment and research
9 communities in identifying data needs in establishing a MOA.
10
- 11 13. It is concluded that a qualitative scheme for the evaluation of mutagenic potential
12 is of considerable value in the application of the framework and that updating of
13 the IPCS scheme is recommended.
14
- 15 14. It should be possible to extend the framework to non-cancer endpoints and further
16 work on this is recommended.
17

1 **References**

2

3 Cohen M, Meek ME, Klaunig JE, Patton DE, Fenner-Crisp PA (2003) The human
4 relevance of information on carcinogenic modes of action: an overview. *Critical Reviews*
5 *in Toxicology*, 33(6): 581-589.

6

7 Committee on Carcinogenicity (COC) (2004). Guidance on a Strategy for the Risk
8 Assessment of Chemical Carcinogens, Department of Health, United Kingdom.

9

10 IPCS (2000) *Scoping meeting to address the human relevance of animal modes of action*
11 *in assessing cancer risk, Carshalton, United Kingdom, 8-10 November 2000*. Geneva,
12 World Health Organization, International Programme on Chemical Safety.
13 <http://www.who.int/ipcs/methods/harmonization/areas/cancer/en/index.html>

14

15 IPCS (2004) *Report of the first meeting of the Cancer Working Group, Arlington,*
16 *Virginia, USA, 3-5 March 2004*. Geneva, World Health Organization, International
17 Programme on Chemical Safety.
18 <http://www.who.int/ipcs/methods/harmonization/areas/cancer/en/index.html>

19

20 IPCS (2005) *Record of the Cancer Framework Workshop, Bradford, United Kingdom,*
21 *21-23 April 2005*. Geneva, World Health Organization, International Programme on
22 Chemical Safety.
23 <http://www.who.int/ipcs/methods/harmonization/areas/cancer/en/index.html>

24

25 National Research Council (1983) *Risk assessment in the federal government. Managing*
26 *the process*. National Academy Press, Washington, DC.

27

28 Meek ME, Bucher JR, Cohen SM, Dellarco V, Hill RN, Lehman-McKeeman LD,
29 Longfellow DG, Pastoor T, Seed J, Patton DE (2003) A framework for human relevance
30 analysis of information on carcinogenic modes of action. *Critical Reviews in Toxicology*,
31 33(6): 591-653.

1

2 Preston JR and Williams GM (2005, in press) DNA-reactive Carcinogens: Mode of
3 Action and Human Cancer Hazard. *Critical Reviews in Toxicology*.

4

5 Slikker W Jr, Andersen ME, Bogdanffy MS, Bus JS, Cohen SD, Conolly RB, David RM,
6 Doerrner NG, Dorman DC, Gaylor DW, Hattis D, Rogers JM, Setzer RW, Swenberg JA,
7 Wallace K (2004). Dose-dependent transitions in mechanisms of toxicity: case studies.
8 *Toxicol Appl Pharmacol* 20:226-294.

9

10 Sonich-Mullin C, Fielder R, Wiltse J, Baetcke K, Dempsey J, Fenner-Crisp P, Grant D,
11 Hartley M, Knaap A, Kroese D, Mangelsdorf I, Meek E, Rice J, Younes M (2001) IPCS
12 Conceptual Framework for Evaluating a Mode of Action for Chemical Carcinogenesis.
13 *Regulatory Toxicology and Pharmacology*, 34 (2): 146-152.

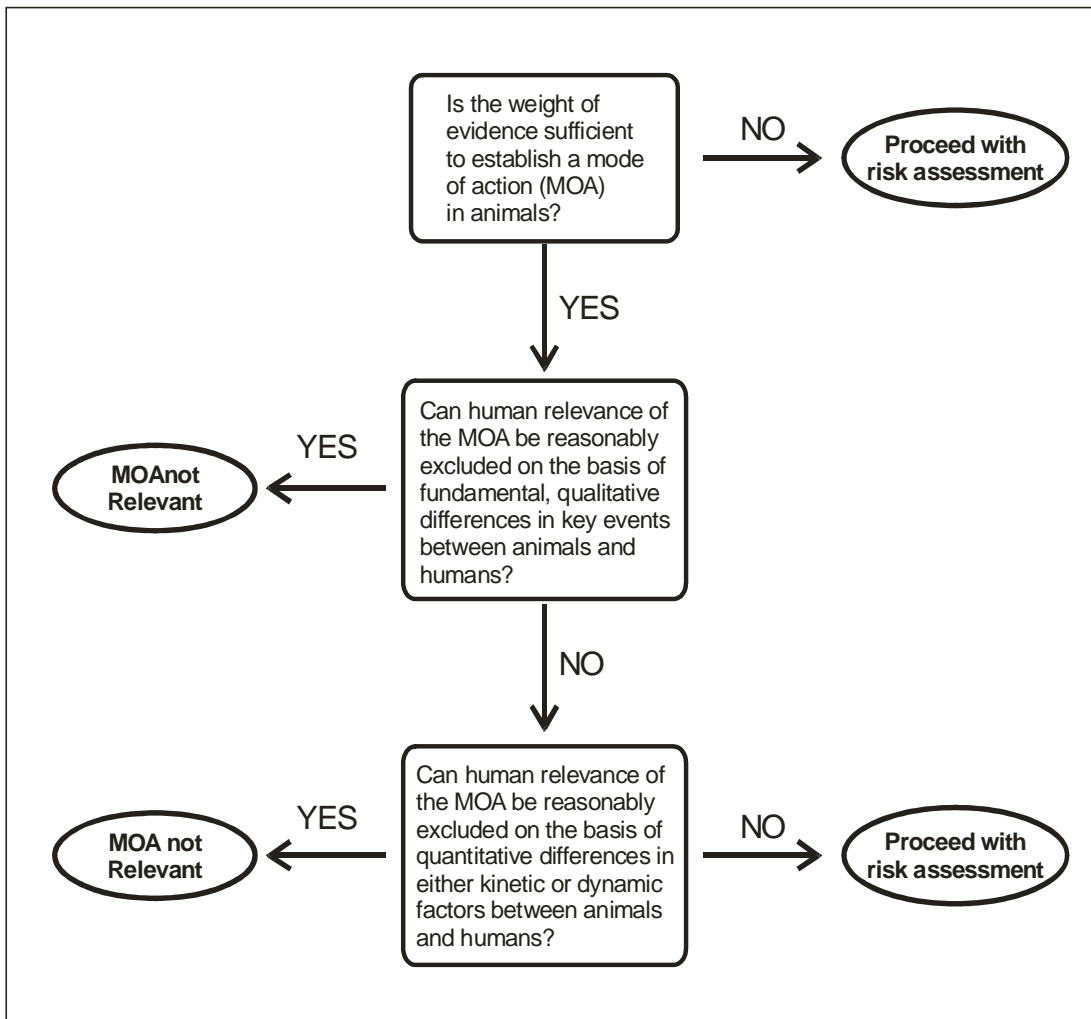
14

15 US Environmental Protection Agency (1999) *Guidelines for carcinogen risk assessment*
16 *(review draft)*. Risk Assessment Forum, Washington DC, NCEA-F-0644.

17

18 US Environmental Protection Agency (2005) *Guidelines for carcinogen risk assessment*.
19 Risk Assessment Forum, Washington DC, EPA/639/P-03/001F.

1 FIGURE 1. IPCS general scheme illustrating the main steps in evaluating the human
 2 relevance of an animal MOA for tumour formation. The questions have been designed to
 3 enable an unequivocal answer YES or NO, but recognizing the need for judgment
 4 regarding sufficiency of weight of evidence. Answers leading to the left side of the
 5 diagram indicate that the weight of evidence is such that the MOA is not considered
 6 relevant to humans. Answers leading to the right side of the diagram indicate either that
 7 the weight of evidence is such that the MOA is likely to be relevant to humans or that it is
 8 not possible to reach a conclusion regarding likely relevance to humans, due to
 9 uncertainties in the available information. In these cases, the assessment would proceed
 10 to risk characterization. It should be noted that only at this stage would human exposure
 11 be included in the evaluation.
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