RISK: Health, Safety & Environment (1990-2002)

Volume 8 | Number 4 Article 3

September 1997

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Introduction

The hazard identification stage of cancer risk analysis presents an interesting problem in the interaction between science, philosophy and the process of decision. This stage is often highly debated since the process of reasoning is primarily qualitative; the results "trigger" the other stages of analysis; the mere act of classifying a substance as a carcinogen is apt to increase public and regulatory pressure for control; and, with the different fields of science that must interact, significant differences in standards of evidence and reasoning can be used.

Regulatory agencies and scientific organizations have attempted to provide quasi-formal guidelines within which hazard identification for carcinogens may be performed in a way that recognizes these issues. An example is the recently released proposal for guidelines on carcinogenicity assessment from the Environmental Protection Agency (EPA),[1] to assist analysts in classifying substances into various categories of carcinogenicity based on available evidence.

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* This research was supported in part by the U.S. Environmental Protection Agency (EPA), Office of Health and Environmental Assessment of ORD. This paper should not be construed as representing the Agency's views or position.

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1 Environmental Protection Agency (EPA), Proposed Guidelines for Carcinogen Risk Assessment; 61 F.R. 17960 (1996).

Table 1
Categories of Carcinogenicity Claims Used by EPA

Category	*Criteria for Classification in the Category*
A	Human Carcinogen Sufficient epidemiological studies
B	Probable Human Carcinogen Limited epidemiological studies and sufficient animal studies (B1); or inadequate epidemiological but sufficient animal studies (B2)
C	Possible Human Carcinogen Limited animal studies and no human studies
D	Not Classifiable as to Human Carcinogenicity Inadequate human and animal studies
E	Noncarcinogenic in Humans No evidence of carcinogenicity in adequate human and animal studies

The key judgment to be made in such classifications is whether the evidence is sufficient to classify a substance as a human carcinogen, sufficient to classify a substance as a carcinogen in animals but limited with respect to human carcinogenicity, or insufficient to classify the substance at all. The EPA provides loose guidelines for the task of determining if a substance is a human carcinogen with sufficient evidence, the primary guideline being well-conducted human epidemiological studies. How evidence is to be used to classify a substance as an animal carcinogen and/or suggestive of human carcinogenicity, and how various bodies of evidence other than epidemiological data are to be united to produce a final judgment, are not specified other than to call for the use of all such evidence.

The goal of assessment guidelines is to provide a framework which draws on the expertise of many disciplines, makes use of diverse bodies of information pertinent to judging carcinogenicity, provides clear rules for reaching and/or justifying decisions needed to classify substances, and allows at least a limited role for expert judgment. While these goals are agreed to be desirable, the existing guidelines for conducting carcinogen hazard identifications leave significant conceptual and methodological gaps in providing a philosophically rigorous framework for assessing evidence and justifying conclusions.

The position of agencies and scientific experts typically has been that it is not possible to develop a completely formal method for assessing the carcinogenicity of a substance. This seems a correct view, recognizing that much scientific work, especially mandated science (in which the time available for rigorous exploration of unresolved scientific issues often is shortened), ultimately must rest on expert judgment. Still, there is a need for better guidance on how these judgments are to be formed and, of equal importance in a regulatory setting, justified or warranted. The recent rulings on Daubert principles (legal guidelines as to how "good" and "junk" science are to be distinguished in courts) makes the need for guidance more pressing, since the lack of a framework for assessing the quality of scientific judgments leaves the interpretation of Daubert principles open to excessive subjectivity and to the possibility that the interpretations will be driven more by strategic positions than by valid epistemic arguments.

Guidelines should help risk analysts understand the rational basis for their judgments of carcinogenicity; understand the rational basis for alternative judgments; isolate the reasons for differences in judgment between individual analysts; and aid decision-makers in understanding these features in the final analysis. They should also help the analyst relate personal reasoning to norms of rationality established either by the larger scientific community, by scholars in rationality, or by the policy community making use of the analysis. In this paper, we present a quasi-formal framework for reaching judgments of carcinogenicity in a manner that draws clear attention to the process of reasoning towards those judgments. The framework has features in common with logic-tree analysis in the sense that the process of reasoning proceeds from lower-order judgments to higher-order claims. However, the framework is built with explicit recognition that judgments formed at nodes of a logic tree ultimately involve a process of expert reflection and debate over principles of choice. The goal is not to lessen the role of expert judgments, but rather to provide a procedure through which the rationality of those judgments may be understood by experts and presented to decision-makers.

The framework uses recent advances in carcinogenicity theory and in the philosophies of rationality and epistemology to structure debates

on claims made on the carcinogenicity of substances in humans. With respect to the use of carcinogenicity theory to structure at least the general flow of scientific judgments and the bodies of evidence useful in reaching those judgments, the framework is similar to those developed recently by other researchers and by the EPA. The key difference lies in the way in which the present framework focuses attention explicitly onto the philosophical principles of rationality underlying judgments, principles rarely discussed in scientific debates.

Taken together, these organizing theories and philosophies provide a framework for analyzing or deconstructing scientific judgments in a way that is tractable to both the scientific and policy communities. The resulting framework should be viewed as an intermediate ground between these two communities, focused on issues of both science and science policy. It "deconstructs" the scientific rationale leading to expert judgments of carcinogenicity, allowing the regulatory, policy and legal communities to understand the particular rationale used in specific assignments of carcinogenicity.

Principles of Rational Analysis

We begin by asking: *What is the nature of rationality and how might this be formalized into a framework useful for judging carcinogenicity?* A central assumption here is that hazard identification should be rational if it is to satisfy demands for scientific accuracy and precision, for philosophical soundness, and for the legal requirement that decisions follow a "hard look" at a problem and not be arbitrary and capricious. The many schools of thought concerning rationality may be placed usefully into two broad groups:[2]

The Classical School of Rationality. Rationality is considered a matter of deduction of the carcinogenicity of a compound from foundational bodies of data reduced to observation statements. This deduction follows the rules of logic, is capable of being "programmed" in the form of well-defined algorithms that are valid universally and is completely open to review.

The Dialogical School of Rationality. Rationality is considered the result of a process of reasoned debate. Debate concerns not only the strength of logical deductions, but also the meanings of terms such as

2 Harold Brown, Rationality (1988).

"evidence", "reasoning", "truth", etc. As summarized by Bernstein,[3]

> central to this new understanding is a dialogical model of rationality that stresses the practical, communal, character of this rationality in which there is choice, deliberation, interpretation, judicious weighing and application of universal criteria, and even rational disagreement about which criteria are relevant and most important.

The dialogical school recognizes that scientific debates follow what Toulmin[4] calls "warrants", meaning lines of reasoning that are not conclusive (i.e. not fully logical) but are accepted as sufficiently "reasonable" to justify at least tentative carcinogenicity claims.

We have chosen deliberately to develop here the framework for analysis based on the dialogical position. We believe it best corresponds to the modern conception of science within philosophy. One example of the application of this philosophy to problems of risk analysis is Schrader-Frechette's conception of scientific proceduralism[5] in which the rationality of science owes as much to the process of scientific debate as it does to the application of formal rules for deduction.

This debate allows flexibility needed to encompass different opinions about the quality and relevance of data, the quality of theories, and the nature of proof in science, while also ensuring that judgments made by individual scientists or groups are not arbitrary and capricious. Expert judgments remain an essential part of dialogical rationality, but they are constrained by the framework for dialogue demonstrating the reasonableness of those judgments in light of specific bodies of evidence and explicit rules of reason. Central to both schools of rationality is an insistence on stating the reasons for claims and demonstrating that those reasons are sufficient to justify the claim.

What are the issues around which this dialogue must be constructed if a hazard identification is to be considered rational? Rational dialogues for hazard identification may be structured around the following principles, taken in part from the writings of Bunge[6] on rationality and philosophy of science:

3 Richard Bernstein, Beyond Objectivism and Relativism (1983).

4 Stephen Toulmin, The Uses of Argument Analysis (1958).

5 Kristen S. Shrader-Frechette, Risk and Rationality (1991).

6 Mario Bunge, *Seven Desiderata for Rationality,* in Rationality: The Critical View (J. Agassi & I. Jarvie eds. 1987).

(1) *Foundationalism.* The quality of observational claims ("observation statements" in the language of logical positivism) for all data used in reaching a judgment should be assessed and shown to be of sufficient quality to justify their use as a foundation in further deductions. This is one example of what Bunge refers to as the epistemological principle in rationality. Satisfying this principle requires consideration of the degree to which the data used in a hazard identification result from studies that are of sound scientific and statistical design, allowing them to form the basis for reliable observation statements and further inference.

(2) *Deducibility.* Complex judgments should be shown to follow deductively from prior, and simpler, judgments to the degree possible. Bunge refers to this as the logical principle in rationality. Satisfying this principle requires consideration of the degree to which a complex judgment that a substance is (or is not) a carcinogen follows reasonably from simpler judgments rooted more firmly in the primary data (such as the judgment that the substance causes mutation).

(3) *Completeness.* All bodies of data pertinent to a carcinogenicity judgment should be considered, with all implications of those data. The goal is to confront the full, and potentially contradictory, body of evidence, rather than only assembling evidence in support of a particular judgment. The goal also is to determine the implications of missing evidence judged a priori to be essential in fully warranting a claim.

(4) *Ontological Rigor.* All bodies of evidence and their potential implications should be developed from a review of the best available scientific theories of carcinogenesis and the role of specific bodies of data within those theories. Bunge refers to this as the ontological principle in rationality.

(5) *Conceptual Clarity.* The meanings of all terms used in a judgment should be clear and conform to current scientific useage. Satisfying this principle requires consideration of the meaning of terms such as "carcinogen", "mutagen", "promotion", etc. The goal is to ensure that disagreements between experts are not arising simply over linguistic differences rather than in differences in ontology.

(6) *Methodological Rigor.* Any framework of analysis should provide some methodological structure which guides the process of

making judgments. A failing of existing guidelines for judging carcinogenicity is that they call for the use of all pertinent bodies of data and expert judgments without providing a methodology by which these goals are to be met.

(7) *Orientation Towards Goals.* The analysis should address all questions whose answers are thought to be valuable by the analyst. In the case of carcinogen hazard identification, the questions considered in the present framework include: Can it be said that the substance is a carcinogen? Can it be said that the substance is not a carcinogen? In what sense is the substance a carcinogen? Under what conditions is it a carcinogen? Under what conditions is it not a carcinogen? What is the epistemic status (i.e. degree of evidential support) for any of these claims? Bunge refers to this as the valuational principle.

(8) *Practicality.* The analysis should produce answers to the questions above in a reasonable length of time and given a reasonable allocation of resources. It would be irrational if the analysis took so long as to result in "paralysis by analysis", since one of the central goals here is to provide information useful to policy makers.

(9) *Sufficiency of Reason.* All judgments of carcinogenicity should be shown to follow reasonably from the available data and the lines of reason by which those data are used to draw conclusions. This assignment of "sufficiency of reason" should include consideration of the quality of data and the quality of any additional assumptions (or background premises)[7] that must be introduced in using the data in supporting a particular claim. It should also include consideration of the reliability of basic categories of reasoning from evidence (called relevance strategies and defined in the next section).

(10) *Consistency.* Principles of reasoning should be applied consistently throughout an analysis and between different analyses, or reasons should be given for any changes. The framework for analysis should draw attention to any inconsistencies by requiring an explicit judgment about the degree to which this consistency principle is satisfied. This consistency might be found in ontological and/or epistemological positions adopted in the analysis.

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7 Helen Longino, Science as Social Knowledge (1990).

Basic Definitions

We turn now to the issue of conceptual clarity: *What are the basic terms that must be understood to use the framework of analysis presented here?* Details of definitions may change between analysts, and the framework does not require any particular formal definition to be useful. Still, these are the definitions adopted by the authors in developing the framework and should prove relatively uncontentious.

Claim of Carcinogenicity. *One of the claims made as result of the hazard identification.* The separate claims are described in a later section. For each claim, it may be determined that the substance being examined has the characteristic (the judgment P); that the substance does not have the characteristic (the judgment not P); or that the determination cannot be made based on available evidence (indeterminate).

Epistemic status. *A qualitative assignment (high, medium, low or no) of the degree to which a claim of carcinogenicity is supported coherently by available well-founded evidence used in appropriate lines of reasoning.* It includes consideration of the quality of the data, the degree to which reasoning conforms to rules of logic, and the quality of background assumptions called for in the lines of reasoning (these background assumptions usually arise from the set of axioms underlying theories of carcinogenicity). Epistemic status is a measure of the strength of the warrant for a claim.

Data item. *Any specific measurement or set of measurements of an objective property of either a substance, the organism exposed to that substance, or the environment within which that exposure takes place, and which is useful as a foundation for inferences of carcinogenicity.*

Data category. *One of the basic classes of data needed to draw inferences of carcinogenicity.* These classes are introduced as a means to bring order to a potentially large range of data by collecting data according to their function within lines of reasoning, as discussed in more detail below.

Completeness. *A qualitative assignment (high, medium, low or no) of the degree to which data items used in the analysis adequately represent the full body of data items available in a data category.* The highest assignment of completeness is obtained when all available data

are used, or when the data used are known to be representative of those not used. The intent of judging completeness is to ensure that the analyst does not bias data selection inadvertently or to support pre-established conclusions.

Utility. *A qualitative assignment (high, medium, low or no) of the ability of a study to accurately and precisely measure the data item it reports.* The utility of a data item is a measure of the foundational qualities of that item. The highest assignment of utility is obtained when a study follows established protocols, satisfies strong statistical criteria, and the effect measured is shown to be causally related to exposure to the substance. Utility is not a measure of the degree to which the data support any final conclusions on human carcinogenicity, but rather a judgment that the data can be used to draw conclusions about the particular aspect of the process leading to carcinogenicity they originally were developed to address.

Strength of Effect. *A summary of the effect observed, such as the appearance of tumors;* a statement of the magnitude of the effect. It is not a judgment about whether a study displaying that effect is of sufficient quality; that judgment was made previously based on utility.

Relevance Strategy. *A basic category of lines of reasoning by which data are related to specific claims of carcinogenicity.* "Relevance" implies that the data are useful as premises appearing in one or more processes of deduction used in warranting a claim, usually in conjunction with background premises. Options are summarized below.

Background Premises. *Additional assumptions that must be introduced if a given body of data is to be used as a warrant for a particular claim of carcinogenicity.* These usually are found in theories which give the data meaning and allow them to be used in drawing inferences about carcinogenicity.

Intellectual Obligation. *A qualitative assignment (high, medium, low or no) of the degree to which a particular category of reasoning (relevance strategy) must be available and factored into a claim of carcinogenicity if that claim is to have high epistemic status.* Note that these requirements are not the same. The first is based on the degree to which the analysts requires that a particular relevance strategy be available in performing an analysis. The second is based on the degree

to which the analyst must weight the results of this strategy if available. It is permissible for an analyst to insist that a relevance strategy be weighted strongly when available, and yet not consider the epistemic status of a claim weak when that strategy is not available (although other analysts may insist that this position is incoherent or inconsistent).

Coherence. *The degree to which the same conclusion about a claim of carcinogenicity is reached from different perspectives.* These different perspectives might arise from different data items, different data categories, different relevance strategies, or different claims of carcinogenicity. Coherence may be at two levels. The lowest level is extant coherence in which the conclusions are the same from each of the existing lines of reasoning for which the necessary data are available. A more strict criterion of coherence is ideal coherence in which it is shown not only that conclusions are the same from all existing lines of reasoning (therefore providing extant coherence), but that these existing lines of reasoning include all lines deemed necessary a priori in fully warranting a claim of carcinogenicity.

Context. *The complete physical, chemical and biological setting within which the carcinogenicity of a substance is being judged.* Central to the idea of a context is the belief that a substance may be carcinogenic in some settings but not necessarily in others. These settings include factors related to the substance (e.g. dose and dose-rate), the organism (e.g. sensitivity), and the presence of other environmental conditions (e.g. concurrent exposures). Claims of carcinogenicity are judged within a given context. If the context is the one of interest (i.e. humans), the claims are in the target context. If the context is not the one of interest, the claims are in an observational context.

Intracontext Extrapolation. *Extrapolation of claims of carcinogenicity from within a context, usually from one level of exposure to another.*

Intercontext Extrapolation. *Extrapolation of claims of carcinogenicity from an observational context to a target context.*

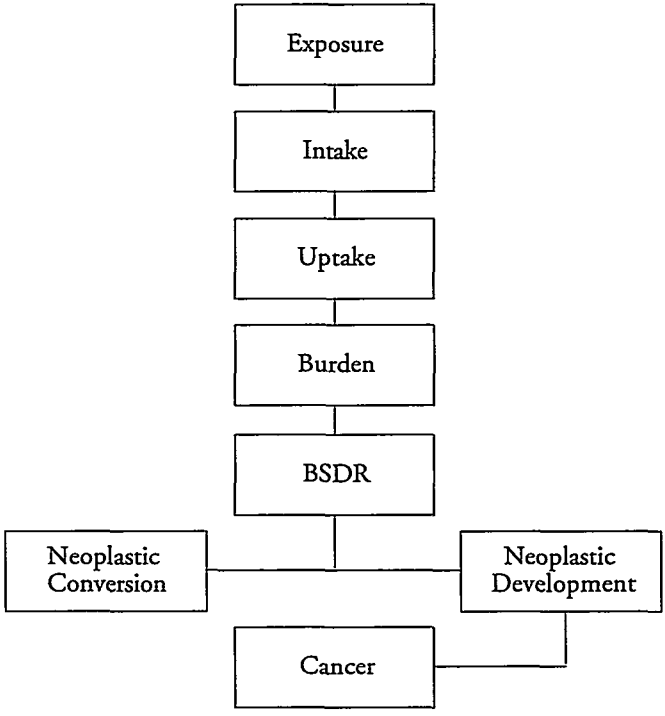
Extrapolation Premises. *The set of assumptions that must be used in extrapolating from one context to another, described below.*

An Ontology of Carcinogen Classification

We now ask: *How might the scientific study of carcinogenicity be used to provide an ontologically sound framework for selecting pertinent data and showing its relevance to claims of carcinogenicity?* A large number of mechanistic theories of carcinogenicity exist;[8] it seems unreasonable to confine the framework to any particular theory. In fact, a goal of the framework should be to assess the validity of competing theories in drawing inferences about the carcinogenicity of a substance. The framework should be flexible to allow modification as understanding of carcinogenesis evolves.

Figure 1[9]

The Ontology of Carcinogenesis Adopted in This Framework for Analysis



8 J. Carl Barrett & Richard W. Wiseman, *Cellular and Molecular Mechanisms of Multistep Carcinogenesis: Relevance to Carcinogen Risk Assessment,* 76 Envtl. Health Persp. 65 (1987); Gary Williams & John Weisburger, *Chemical Carcinogenesis,* in Toxicology (1991); and Samuel Morris, Cancer Risk Assessment: A Quantitative Approach (1990).

9 The upper part of the figure displays the reasoning from exposure to BSDR. The lower part shows the reasoning from BSDR to a Neoplasm (Adapted in part from Fig. 5-1, Williams & Weisburger, *supra*).

Still, some ontological choices must be made about the broad features of carcinogenesis so as to provide an initial methodological framework for analysis. The authors have adopted the following minimal assumptions about carcinogenesis; also see Figure 1.

(1) Cancer results from the action of a substance or its metabolites on specific targets in the organism, although there may be multiple targets and multiple mechanisms of action.

(2) Cancer develops in more than one stage (i.e. is a *multistage process).* These stages include at least *neoplastic conversion* and *neoplastic development.* The identification of these two stages with initiation, promotion and progression is not required here, but that possibility is not excluded by the framework of analysis.

(3) The mechanisms of action may be either *genotoxic* (operating directly on the genetic material of cells, such as on DNA) or *non-genotoxic* (operating on structures other than genetic materials, such as on gap junctions in intercellular communication).

(4) The action of the substance is related directly (which does not necessarily mean linearly) to a *biologically-significant dose-rate (BSDR).* The BSDR is related to the concentration of the active form of the substance or its active metabolite(s) at the site of the target.

(5) The BSDR is related to the exposure through *pharmacokinetic properties* which are a function of the substance, the organism and the presence of other environmental conditions (including exposure to other substances). The pattern of reasoning is from *exposure intensity* (e.g. concentration of the substance in the environment), to *exposure* (which includes exposure intensity and length of exposure), to *intake* (which is a measure of the amount of the substance taken into the body), to *uptake* (which is a measure of the amount of the substance absorbed into the body), to *burden* (which is a measure of the amount of the substance in an organ or tissue), and to *BSDR* (which includes consideration of the role of metabolic activation or inactivation).

(6) A carcinogen produces *transitions* between stages of cancer. If all transitions are produced by a substance, the substance is a *complete carcinogen* within the context of exposure. If only a subset are produced, the substance is a *partial carcinogen* within the context of exposure and will elevate the incidence of cancer only if the other transitions are produced by other causes. If the substance must join

physically with a second substance to produce the active substance (e.g. producing a third chemical), the substance is a *mixer* within the context of exposure. If the substance doesn't produce transitions, but causes cellular changes that allow a second substance to cause transitions, the first substance is a *helper.*

These six basic assumptions about carcinogenicity lead to a hierarchy or taxonomy of claims of carcinogenicity. The individual bodies of data described in the next section act as part of the warrants for these claims through the relevance strategies discussed in a still later section. First in the hierarchy is the claim that the substance increases the incidence of cancer within the context. Next in the hierarchy is the classification of the substance as a complete carcinogen, a partial carcinogen, a mixer and/or a helper. Next in the hierarchy is the specification of the substance into the two stages, either neoplastic conversion or neoplastic development. Finally, the mechanism of action may be given as either genotoxic or non-genotoxic.

As the analyst moves from the top to the bottom of the hierarchy, the details of the mechanism of action become progressively defined. The conclusions at the lower levels support the claims at the higher levels by providing rational support through claims to understanding mechanisms, which is one of the hallmarks of scientific rationality. They also help to specify the conditions (or context) within which a substance acts as a carcinogen. It also should be the case that claims at different levels are coherent, at least if the analyst judges coherence to be an important measure of epistemic status. For example, the claim that a substance acts at the stage of neoplastic conversion may be taken as incoherent with the claim that it acts through a non-genotoxic mechanism if the analyst believes that neoplastic conversion means initiation and that initiation is caused by direct action on DNA (an assumption that is not inherent in the framework developed here but which is allowed within that framework).

Organizing the Data

We now ask: *How might the data be organized so as to show their role in relevance strategies and ensure that all pertinent bodies of data are assessed, while not overwhelming the analyst with a potentially*

large and unstructured mass of information? We have chosen to divide data into six functional categories (i.e. catgeories based on their functions within lines of reasoning) which will be related later to the relevance strategies, background premises and/or extrapolation premises. The bodies of data associated with each are provided here only as examples. The framework of analysis draws the analyst's attention to these, but others may be added.

(1) *Tumor Response.* This includes all bodies of data in which some characteristic of tumors following exposure is measured directly. These characteristics are incidence, prevalence, multiplicity, time-to-appearance, age-at-appearance, initiation or promotion.

(2) *Biophysical Effect.* This includes all bodies of data in which a biological change leading to, but not completely identical with, cancer is measured. These data include measurements of hyperplasia, DNA adducts, oncogene activation, interference with intercellular communication, ability to metastasize, concentration of tumor growth factor, DNA breakage, chromosomal aberrations, site-specific mutations, mutagenicity, cellular transformation, relevant alterations in RNA structure or function, appearance of cancer marker proteins, alterations in antigens, presence of preneoplastic lesions, alterations of cellular architecture, alteration of distribution in histological types or differentiation, cytotoxicity, or hormonal alterations.

(3) *Host Characteristics.* This includes all bodies of data concerning the susceptibility of a host to cancer following delivery of a biologically significant dose-rate. These data include DNA repair rates, DNA repair specificity, density of repair enzymes, repair kinetics, activation/inactivation of repair processes, background rates of transition, presence of a target organ/tissue, or presence of a specific carcinogenicity mechanism or pathway.

(4) *Pharmacokinetic Properties.* This includes all bodies of data on the relationship between exposure and biologically significant dose-rate. These data include frequency and volume of inhalation, rate of ingestion, lung morphometry, lung physiology, epithelial integrity, deposition fractions, absorption fractions, partition coefficients, organ masses, removal half-times, measures of facilitated transport, first pass excretion, first pass metabolism, cardiac output, organ perfusion, pore

sizes, metabolic reaction kinetics, substrate density, renal flow rate, renal permeability, diffusion coefficient, neutrophilicity, adduct binding coefficient, intake rates, uptake rates, or organ burdens.

(5) *Concurrent Environmental Conditions.* This includes all bodies of data on the environmental conditions present during exposure to the substance of interest, at least as these data are pertinent to defining the context of exposure. These data include attachment to particles, presence of oils during administration, presence of other substances, or conditions of stress.

(6) *Structure-Activity Relationships.* This includes all bodies of data on substances other than the substance of interest, but possessing similar structural characteristics important to carcinogenesis.

The Relevance Strategies

Now: *How can the analyst employ specific bodies of data in drawing inferences about claims of carcinogenicity, while recognizing the existence of alternative lines of reasoning?* We have chosen to organize different lines of reasoning into five relevance strategies. Different analysts might use different relevance strategies, but the following strategies are most commonly discussed in epistemology, philosophy of science and risk analysis. Throughout the framework, analysts are asked both to justify their particular selection of relevance strategy and to reflect on the strategies they did not select. The goal ultimately is to confront conclusions drawn from all relevance strategies and to assess the coherence across them.

(1) *Direct Empirical.* This line of reasoning uses direct observations of the effect of interest (such as increasing the incidence of cancer) within the context and level of exposure of interest in making a claim. Clearly, only *tumor response* data may form the foundation for this line of reasoning. In addition, the tumor response data must be in the context of interest. If the target context is human, tumor response data from rats does not constitute direct empirical evidence for the target context, although it does constitute direct empirical evidence for carcinogenicity in the rat observational context. The necessary background premises for direct empirical evidence are that the data was produced in a context in which the relationship between exposure and

BSDR, as well as the relationship between BSDR and effect, is identical to that defining the context in which claims are being made. These background premises are supported by data from *biophysical effects, pharmacodynamic properties, host characteristics and concurrent environmental conditions.*

(2) *Semi-Empirical Extrapolation.* This line of reasoning uses observations of the effect of interest at exposures above those of interest, but within the same context. A pattern is noted in the relationship between exposure and effect, and this pattern is "followed" or "extrapolated" to the level of exposure of interest. The major background premises are those for the direct empirical strategy, as well as the premise that the pattern used for extrapolation is either well established by theory or directly observed in data. Again, only *tumor response* data may form the foundation for this line of reasoning, although the other categories of data may prove useful in supporting the claim that the pattern is to be expected based on understanding of the biological mechanism of action (i.e. etiologic theory).

(3) *Empirical Correlation.* This line of reasoning uses observations of effects other than tumor production. The reasoning is that appearance of these effects correlates with appearance of tumors. No attempt is made to explain why this correlation exists, although a judgment must be made of the strength and specificity of the correlation. The pertinent data are primarily *biophysical effects* (e.g. mutation) and *structure-activity relationships* (e.g. the presence of a bay region), but *pharmacokinetic properties* may also be used (e.g. production of an active metabolite). The background premises involve a demonstration that the conditions in which the correlation was measured previously (and which controls the strength and specificity) also are found in the context for which claims of carcinogenicity are being made in the analysis. Support for the background premises may be found in data on biophysical effects, pharmacodynamic properties, host characteristics, concurrent environmental conditions and structure-activity relationships.

(4) *Theory-Based Inference.* This line of reasoning uses observations of effects other than tumor production. It differs from empirical correlation in that the analyst uses a mechanistic theory of

carcinogenicity to explain why observing (or not observing) the non-tumor effect justifies the claim that the substance is (or is not) a carcinogen. For example, observing mutation could be used as a theory-based warrant for the claim that a substance is a carcinogen if the analyst accepts (with sufficient proof) the theory that one of the transitions to cancer may be produced by mutation of genetic material, and that other transitions will occur with a non-zero probability.

The background premises involve a demonstration that the theory used in drawing the inference is supported within the context of exposure. Other premises are that exposure, intake, uptake, burden, biologically significant burden, and transitions between stages of cancer all are resulting from the presence of the substance within the context for which claims are being made. The pertinent data are *biophysical effects, pharmacodynamic properties, host characteristics, concurrent environmental conditions and structure-activity relationships.*

(5) *Existential Insight.* At times, the analyst may support claims based on expert judgment. This approach is not irrational so long as it is believed that experts possess knowledge that cannot be demonstrated by any particular process of reasoning. It is equivalent to Polanyi's tacit knowledge.[10] To the degree rationality is deemed to require public disclosure of reasons for claims, this strategy may fail to satisfy criteria of rationality. The background premises involve establishing that the expert falls into the group of experts likely to have developed such knowledge based on pertinent experience.

The Framework for Analysis

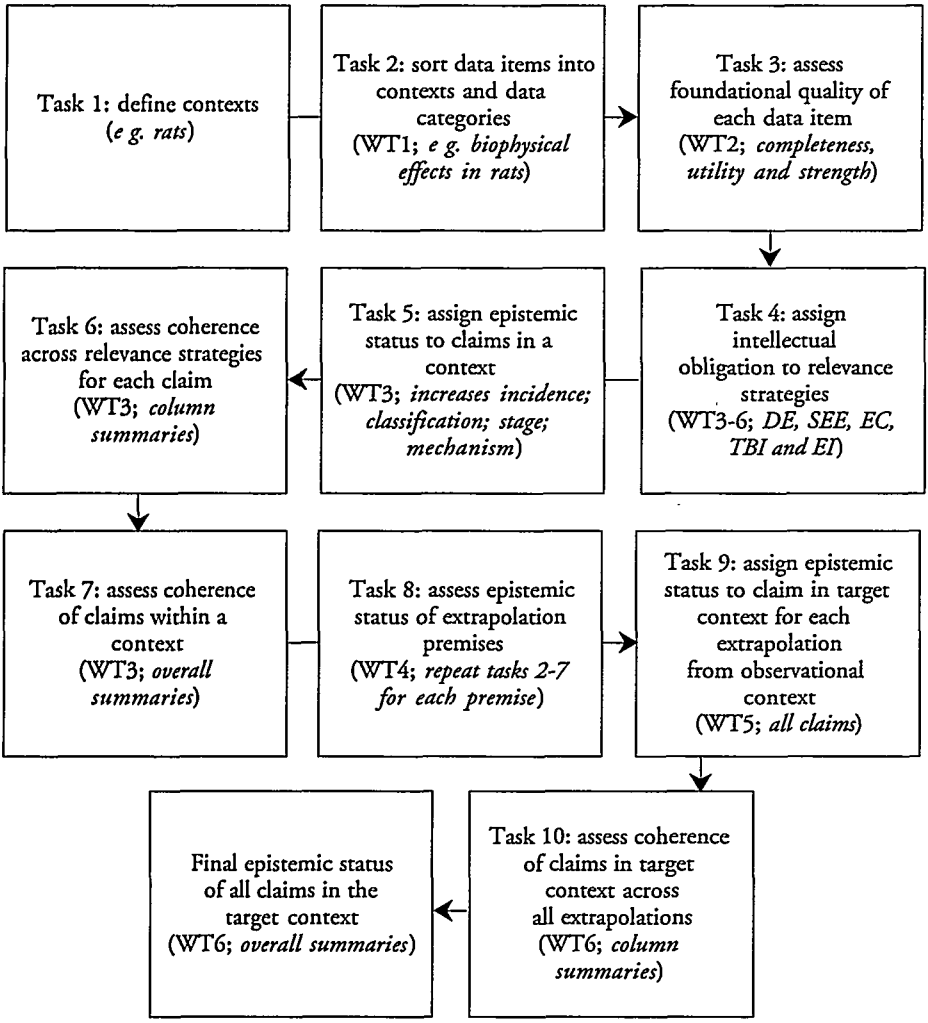
Having established the principles and terms on which the framework for analysis will be constructed: *What is the specific form a methodology might take for assessing the epistemic status of claims of carcinogenicity?* Whatever the form, it should draw attention to each of the considerations raised earlier, should require specific judgments related to those considerations, should make it clear how those judgments play a role in arriving at the final assignment of the epistemic status of a claim, and should make it clear how that assignment might differ if other judgments had been made. It should cause the analyst to provide both scientific and philosophical positions

10 Michael Polanyi, Personal Knowledge (1958).

necessary to establish the reasons for claims, without necessarily causing an infinite regress in which continued questioning of reasons to deeper levels is pushed to extremes that impede the formation of judgments (and go against the goal of practicality).

Figure 2[11]

The Series of Tasks within This Framework of Epistemic Analysis



[11] The tasks proceed from defining the contexts; to sorting the data into contexts and data categories; to assessing the epistemic status of claims within each context; to extrapolating from observational to target contexts; to assessing the epistemic status of claims in the target context.

The methodological framework adopted here is based on a series of *working tables* through which the analysis must pass; see Figure 2. The working tables bring the analyst through each of the judgments that must be made, organizing these judgments into a final assignment of the epistemic status of particular claims of carcinogenicity within specific target contexts. Each claim of carcinogenicity is assessed first within each separate observational context using only data items generated from studies satisfying the conditions of that context. Extrapolation premises then are established for each necessary case of extrapolation from an observational context to a target context. The extrapolations then are carried out and an overall assessment made of the epistemic status of claims of carcinogenicity in the target context.

This section of the paper provides a highly abbreviated example of the working tables, taken from an earlier feasibility study designed to test the usefulness of the methodology in judging the carcinogenicity of formaldehyde.[12] The feasibility study used only a very limited set of data since the intent was to test the methodology rather than to perform an actual hazard identification for formaldehyde. The example is provided here only to show what the working tables look like and how they are used. No conclusions should be drawn concerning the validity of the specific judgments shown in the tables, or the sufficiency of those judgments as a basis for regulatory decisions.

The working tables are organized into a series of tasks producing answers to the following questions; see Figure 2:

Task 1: *What are the observational and target contexts to be considered in the analysis?* Working Table 1 (WT 1) requires that the analyst define the various contexts, giving a clear description of the conditions of the organism, substance and environment that must be satisfied if a particular data item is to be considered as having been generated in a given context. This description is provided in the heading to each table, with one table for each context. The goal here is to select a relatively small number of contexts in which summary

12 Douglas J. Crawford-Brown & Kenneth G. Brown, *Hazard Identification in Carcinogen Risk Analysis: An Integrative Approach. Parts I & II.* (1992). Also Douglas J. Crawford-Brown, Jeffrey Arnold & Kenneth G. Brown, *Hazard Identification in Carcinogen Risk Analysis: An Integrative Approach. Part III. An Application of the Methodology: Formaldehyde in Air* (1994) (Reports to EPA; may be obtained from the authors).

judgments of carcinogenicity may be made (thereby organizing the data into manageable collections), without losing essential information about the unique characteristics of individual studies and their contexts.

Working Table 1
Data for the Target Context; Exposure of Humans to Airborne Formaldehyde at Concentrations Below 2 ppm

Study Number[a]	*Data Category*	*Description*
1	BE	Primary Reference #7 in Table 31 female and 24 male human subjects were grouped into cohorts exposed to formaldehyde vapor in various occupations characterized by exposure to formaldehyde in tobacco smoke and other unspecified routes. Subjects then were evaluated for antibody reaction (serum IgE or IgG) and for whether the presence of antibodies correlated with a history of respiratory and conjunctival symptoms. The low level exposure for histology technicians was 0.64 ppm; for pathology residents from 0.2 to 0.64 ppm; and for medical] residents was unreported. Clinical assessments of antibody formation were made by ELISA detection and by skin challenges followed by subjective expert judgment of the presence of a response.

[a] The study number refers to the order of the study within this context. The primary reference number indexed to Table 1 is provided in the "Description" column.

In the example, the target context is taken as exposure of humans to airborne formaldehyde at concentrations of less than 2 ppm. Observational contexts are the target context, as well as exposure of rats, mice and humans mice to airborne formaldehyde over 2 ppm, as well as in-vitro exposure of human cell lines and in-vitro exposure of nonhuman mammalian cell lines to formaldehyde in solution. The decision to separate human exposures into two concentration categories (above and below 2 ppm) is based on the desire to draw inferences about carcinogenicity at low levels, where the inferences might be different from those drawn at higher levels of exposure. If the goal was simply to ask whether formaldehyde was a human carcinogen at any level of exposure, this separation would have been unnecessary and both human contexts would be put together into a single target context.

Task 2: *What are the data items available in each context and what do they show directly (i.e. with no further inferences required)?* The goal of this stage of the analysis is to assign each data item a reference number for tracking, to determine the appropriate data category for that data item, and to provide a summary observation statement. A separate description is given for each data item in each study placed into each context. In the example shown here, which is for the target context, only a single study (called Study Number 1) is used, with the data on allergic response being placed into the category of biophysical effects (BE). There is a single data item in this study.

Working Table 2
Summary Judgments of the Foundational Quality for Data in WT 1 for the Target Context

Data Category/Item	*Description*	*Completness*	*Utility*	*Strength of Effect*	*Exposure-Specific Effect*[a]
Tumor Response	No study available [NSA]				
Biophysical Effect	Allergic response (BE1.1)	HI	HI	NO	WT2.C12 BE1.1
Pharmacodynamics	NSA				
Host Factors	NSA				
Concurrent Environmental Conditions	NSA				
Related Substances Assessment	NSA				

[a] Refers to the Exhibit Number for the data as described in the text.

Task 3: *What is the foundational quality of each data item in each context?* WT 2 summarizes the judgments of the quality of each data item in each of the six data categories prior to the use of those data in lines of reasoning. In the example shown here, the working table is for the target context. It may be noted that the only data item is in the data category of biophysical effect; that the effect was an allergic response; and that this data item was assigned a label of BE1.1 for indexing (biophysical effect; study 1; data item 1 in that study).

Working Table 3[13]

Summary of the Judgments of Epistemic Status for the Claims of Carcinogenicity

Relevance Strategy	Intellectual Obligation	Claims of Carcinogenicity									
		Increases Cancer Incidence	Classifications(s)				Stage		Mechanism	
			Complete	Partial	Mixer	Helper	NC	ND	GT	NGT
Direct Empirical	HI	NO	NO	NO	NO	NO	NO	NO	NO	NO
Semi-Empirical Extrapolation	ME	NO	NO	NO	NO	NO	NO	NO	NO	NO
Empirical Correlation	ME	NO	NO	NO	NO	NO	NO	NO	NO	NO
Theory-based Inference	ME	NO	NO	NO	NO	NO	NO	NO	NO	NO
Existential Insight	LO	NO	NO	NO	NO	NO	NO	NO	NO	NO
Column Summary		NO	NO	NO	NO	NO	NO	NO	NO	NO
Overall Summary		NO	NO	NO	NO	NO	NO	NO	NO	NO
Direct Empirical	HI	HI	NO	NO	NO	NO	NO	NO	HI	NO
Semi-Empirical Extrapolation	ME	NO	NO	NO	NO	NO	NO	NO	NO	NO
Empirical Correlation	ME	ME	NO	NO	NO	NO	HI	ME	HI	NO
Theory-based Inference	ME	HI	NO	NO	NO	NO	ME	ME	ME	NO
Existential Insight	LO	HI	NO	NO	NO	NO	ME	ME	HI	NO
Column Summary		HI	NO	NO	NO	NO	ME	LO	HI	NO
Overall Summary		HI	NO	NO	NO	NO	ME	LO	HI	NO

13 The top table shows judgments for the Target Context. This utilizes only data in the Target Context as shown in Working Tables 1 and 2. The bottom table is for the Observation Context of rats and is provided here for contrast with the judgments in the Target Context.

The first judgment is of the completeness of the data items in each data category. Here, the assignment of completeness is HI (high) since this one study of allergic effect was the only study identified in a larger literature search of allergic effects noted in this context. The assignment of utility is HI since the study was judged to follow appropriate protocols and to have a sufficient statistical power to detect the examined effects. The assignment of strength of effect is NO since no allergic response was found. Taken together, these three judgments constitute the foundational quality of this data item.

Task 4: *What is the measure of intellectual obligation assigned to each relevance strategy?* All working tables after the second require that this judgment be made. If the principle of consistency is valued highly, the measure of intellectual obligation for a specific relevance strategy should be the same across all working tables and all contexts. In the example shown above for WT 3, we took the epistemological position of a strong empiricist, giving high intellectual obligation to direct empirical reasoning, i.e., the effect of interest must be observed at the level of exposure of interest if the epistemic status of a carcinogenicity claim is to be high, regardless of how well established other lines of reasoning might be. We also assert that expert judgment will not be weighted heavily (low or LO intellectual obligation to existential insight) but the other three relevance strategies should be moderately (medium or ME) weighted in the final assignment of epistemic claim status. Other legitimate assignments are possible.

Task 5: *What is the epistemic status of each claim of carcinogenicity as warranted by each separate relevance strategy within each context?* Each judgment is shown as a separate cell in WT 3. There is a separate working table for each observational and target context. It may be seen in the example WT 3 that the claims of carcinogenicity correspond to the hierarchy of claims described earlier. Columns for claims may be added, subtracted or altered as the ontology provided by scientific theories of carcinogenesis changes and as the analyst finds it useful to distinguish modes of action.

The judgment of the epistemic status of a claim (shown in one of the cells of WT 3) based on a particular relevance strategy depends on the answers to seven questions:

(1) *Which data items identified in WT 1 are appropriate for use in that relevance strategy?* This was discussed in the earlier section on the relevance strategies. For example, the relevance strategy of theory-based inference shown here in WT 3 uses the biophysical effects data on allergic response.

(2) *What is the foundational quality of each of these data items, as summarized in WT 2 (and as addressed in Task 3)?* This foundational quality is given by the composite of the judgments on completeness and utility, both of which were judged to be high in the example of formaldehyde used here. The composite judgment was, therefore, that the foundational quality is high (HI).

(3) *What was observed in this data item?* Here, the observation was that allergic response was not produced following exposure.

(4) *What are the background premises needed for use of these data in this relevance strategy?* The analyst must describe the manner in which background premises, in conjunction with the data items from (2), support the claim. For this example of theory-based inference, the background premises are that exposure was present; an intake of formaldehyde was present; uptake of formaldehyde at the target site for allergic response was present; a burden of the biologically-active form of formaldehyde and, hence, a biologically significant dose-rate was present; that allergic response indicates increased rates of transition between stages of cancer; and that any remaining transitions would be caused by background events.

(5) *What is the epistemic status of each of these background premises and of the theory of carcinogenesis from which they arose?* To be fully supported, data must demonstrate the validity of each premise listed in (3) within the context being examined (here it is the target context). For this example, the background premise suggesting allergic response produces transitions was judged to have low support. Other background premises were judged to be well supported.

(6) *What is the intellectual obligation assigned to this relevance strategy?* This judgment is shown as medium (ME) in the intellectual obligation column in the example WT 3.

(7) *What is the composite judgment of epistemic status for the claim of carcinogenicity under each relevance strategy within this*

context? In the example WT 3, the epistemic status for theory-based inference and the claim that formaldehyde exposure increases the incidence of cancer is NO, meaning that the available evidence, when used in this relevance strategy, provide no warrant for the claim. This judgment might have been reached because the foundational quality of the data item used was poor (NO); because the epistemic status of background premises was poor (NO); or because the strength of the effect was poor (NO). In the example here, the epistemic status was given as NO because no effect was observed, and even if it had been, the premise of an etiologic link between allergic response and carcinogenicity was judged to be poorly established.

The entry of a judgment into this cell relates only to the question of whether formaldehyde in this context *does* increase the incidence of cancer. A separate table is used for the judgment that formaldehyde *does not* increase cancer incidence. An assignment of NO in the example shown cannot be taken as evidence that formaldehyde does not increase the incidence of cancer. It simply says that there is little or no warrant for the claim that it *does* increase cancer incidence based on this relevance strategy and selected data items.

Another issue raised in making these entries is how to treat the existence of competing bodies of data and/or competing theories. The analyst is asked to select and justify one or more of several options for dealing rationally with competing bases for claims. These are to select only the data/theory with the highest epistemic status; to combine data into a single set (a form of meta-analysis); to complete working tables under each combination of data/theories and then make a composite judgment across these different sets of working tables; or to provide weights to each data set and theory and take a weighted average across these before performing each step in the analysis.

Task 6: *What is the composite epistemic status for each claim of carcinogenicity in each context, taking into account all five relevance strategies?* Here, the analyst is judging the coherence of the warrants for a particular claim of carcinogenicity across the relevance strategies. This is shown as the Column Summary judgments in the example WT 3. It is expected that this composite judgment will involve a weighting of the judgments from the separate relevance strategies in proportion to

their respective intellectual obligations. An alternative approach might be to use only the relevance strategy with the highest intellectual obligation. In the example shown here, the composite Column Summary judgment of epistemic status is NO since the judgment was NO for all relevance strategies (indicating high coherence).

Task 7: *What is the composite epistemic status for each claim of carcinogenicity in each context, taking into account all claims?* Here, the analyst is judging the coherence of claims across all claims in the hierarchy (i.e. across all Column Summary judgments). This is shown as the Overall Summary judgments in the example WT 3. This issue was discussed previously when describing the heirarchy of carcinogenicity claims.

Working Table 4
Summary of the Judgments of Epistemic Status for Extrapolation Premises between the Observational Context of Rats and the Target Context

Relevance Strategy	Intellectual Obligation	Exposure to BSDR Conversion	BSDR to Effect Conversion	Host Factors	Environmental Conditions
Direct Empirical	HI	NO	NO	LO	ME
Semi-Empirical Extrapolation	ME	NO	NO	NO	NO
Empirical Correlation	ME	ME	ME	ME	NO
Theory-based Inference	ME	ME	HI	ME	ME
Existential Insight	LO	ME	HI	ME	ME
Overall Assessment		LO	LO	LO	ME

Task 8: *What is the epistemic status of the extrapolation premises needed to extrapolate between each observational context and the target context?* These are established by the ontology of carcinogenicity described earlier. Necessary premises are summarized in WT 4:

Extrapolation Premise 1. The relationship between exposure and BSDR is sufficiently similar in the two contexts that a claim of carcinogenicity in the observational context may be taken as a claim of carcinogenicity in the target context, all other factors equal.

Extrapolation Premise 2. The relationship between BSDR and the effect of interest is sufficiently similar in the two contexts that a claim of carcinogenicity in the observational context may be taken as a claim of carcinogenicity in the target context, all other factors equal.

Extrapolation Premise 3. The host characteristics are sufficiently similar in the two contexts that a claim of carcinogenicity in the observational context may be taken as a claim of carcinogenicity in the target context, all other factors equal.

Extrapolation Premise 4. The environmental conditions (other than the concentration of the substance of interest) are sufficiently similar in the two contexts that a claim of carcinogenicity in the observational context may be taken as a claim of carcinogenicity in the target context, all other factors equal.

It is necessary to address the seven questions appearing in Task 5 for each of the four extrapolation premises. This is shown in the example WT 4 as judgments in the separate cells. The reader should note that this example working table is for the observational context of rats exposed to formaldehyde at any concentration.

Task 9: *What is the epistemic status of each claim of carcinogenicity in the target context when this claim is extrapolated from each observational context?* WT 5 calls for a judgment of the epistemic status of each claim of carcinogenicity in the target context, but based on extrapolation of the claims in WT 3 for a particular observational context. For example, the judgments of claims in WT 3 for the context of rats exposed to formaldehyde is combined with the judgments of the epistemic status of the necessary extrapolation premises shown in WT 4 to produce the judgments in WT 5.

It may be seen that the epistemic status of all claims is NO under the direct empirical relevance strategy, since the rat data are not produced in the target context (violating the meaning of direct empirical reasoning). It might be argued that, to be consistent, the same should be true for claims based on semi-empirical extrapolation. WT 5, however, shows that the analyst has used the rat data to assert that formaldehyde exposure in humans at 2 ppm or less is likely to produce genetic changes, with the epistemic status for this claim being medium (ME). The reason for this choice is that the analyst judged the mechanism of genetic damage to be independent of context. If a second analyst disagreed with this premise, the entry into the cell in WT 5 would be NO.

Working Table 5. Summary of Judgments of Epistemic Status for Carconogenicity Claims In the Target Context Based on Extrapolation from the Observational Context of Rats

Relevance Strategy	Intellectual Obligation	Claims of Carcinogenicity									
		Increases Cancer Incidence	Classifications(s)				Stage		Mechanism	
			Complete	Partial	Mixer	Helper	NC	ND	GT	NGT
Direct Empirical	HI	NO	NO	NO	NO	NO	NO	NO	NO	NO
Semi-Empirical Extrapolation	ME	NO	NO	NO	NO	NO	NO	NO	ME	NO
Empirical Correlation	ME	ME	NO	NO	NO	NO	ME	LO	ME	NO
Theory-based Inference	ME	ME	NO	NO	NO	NO	ME	LO	ME	NO
Existential Insight	LO	ME	NO	NO	NO	NO	ME	LO	ME	NO
Column Summary		LO	NO	NO	NO	NO	ME	LO	ME	NO
Overall Summary		LO	NO	NO	NO	NO	ME	LO	ME	NO

Both a Column Summary and an Overall Summary must then be produced in a manner described in Tasks 6 and 7. A separate version of WT 5 is completed for each pair of observational and target contexts.

In each case, the version of WT 4 used in the extrapolation is specific to that pair of contexts. For the example of formaldehyde used here, five different versions of WT 5 were generated during the analysis.

Working Table 6.
Summary of Judgments of Epistemic Status for Carconogenicity Claims Based on all Instances of Extrapolation from an Observational Context and on the Results of WT 3

Context Number	Claims of Carcinogenicity										
	Increases Cancer Incidence	Classifications(s)				Stage(s)		Mechanism(s)		
		Complete	Partial	*Mixer*	*Helper*	NC	ND	GT	NGT
Intra-Context From Context 12	NO	NO	NO	NO	NO	NO	NO	NO	NO
Intra-Context From Context 5	LO	NO	NO	NO	NO	ME	LO	ME	NO
Intra-Context From Context 6	LO	LO	LO	NO	NO	ME	NO	ME	NO
Intra-Context From Context 11	LO	NO	NO	NO	NO	NO	NO	NO	NO
Intra-Context From Context 13	LO	NO	NO	NO	NO	NO	NO	NO	NO
Intra-Context From Context 14	LO	NO	LO	NO	NO	ME	NO	ME	NO
Column Summary	LO	NO	NO	NO	NO	ME	NO	ME	NO
Overall Summary	LO	NO	NO	NO	NO	ME	NO	ME	NO

Task 10: What is the final epistemic status for each claim of carcinogenicity in the target context, taking into account all routes of inference? There are versions of WT 5 for each observational context, and a version of WT 3 for the target context. Each working table has

produced a judgment of the epistemic status for each claim of carcinogenicity in the target context based on warrants from a different context. The final step is to combine these judgments. This is shown in the example provided as WT 6. The context numbers refer to those assigned in the original report. Context 12 is the target context; Context 5 is rats; Context 6 is mice; Context 11 is humans exposed to greater than 2 ppm; Context 13 is human cell lines; and Context 14 is nonhuman mammalian cell lines.

The Overall Summary judgments from the earlier tables (WT 5 for an observational context and WT 3 for a target context) are entered into the appropriate row of WT 6. Tasks 6 and 7 are then repeated to produce composite judgments as a Column Summary and an Overall Summary. The Overall Summary row then contains the final judgment of the epistemic status of each carcinogenicity claim for the target context. It may be seen from WT 6 that the final judgments are:

(1) The epistemic status of the claim that formaldehyde increases human cancer incidence at 2 ppm or less is LO. This is not to say that the evidence shows formaldehyde doesn't produce cancer at this exposure. Such a judgment requires separate working tables focused on the claim that formaldehyde does not increase the incidence.

(2) The epistemic status of the claims that formaldehyde is a complete carcinogen, is a partial carcinogen, is a mixer, is a helper, acts on neoplastic development, and acts by non-genotoxic mechanisms when humans are exposed at 2 ppm or less is NO.

(3) The epistemic status of the claims that formaldehyde acts on neoplastic conversion and by a genotoxic mechanism is medium (ME). It can be seen that the analyst did not consider the claim that formaldehyde acts on a neoplastic conversion to be incoherent with the assignment of LO to the epistemic status of the claim that formaldehyde increases the incidence of cancer, or with the assignments of NO to the various classifications. This is evident from the fact that the Column Summary and Overall Summary judgments are identical. Another analyst might judge that formaldehyde being a genotoxic agent is further support for the other claims of carcinogenicity, choosing to increase the epistemic status of one or more claims in the Overall Summary.

Discussion

We have provided a framework of working tables and associated tasks by which carcinogenicity judgments for a substance may be assessed rationally. Central to it are the principles that rationality requires explicit consideration of the epistemic status of a claim; that epistemic status is constructed from a review of available data and lines of reasoning in which that data plays a role; and that a proper judgment of epistemic status is formed after reflection on the coherence across competing scientific and philosophic positions.

This framework provides a tool for structuring discussion or debate, in, e.g., Science Advisory Board or National Academy of Sciences committee meetings or in regulatory negotiation. Ideally, individual analysts would complete working tables in relative isolation, allowing each to formulate a personal view on the epistemic status of claims. Individuals then would meet to examine similarities and differences of judgments. Discourse would focus on reasons for differences, locating them in the selection of pertinent data bodies, the development of contexts, judgments of foundational data quality, identification of background premises needed for use of relevance strategies (in the form of theories of carcinogenesis), assignment of epistemic status to premises, assignment of intellectual obligation to relevance strategies, treatment of coherence in the Column or Overall Summaries, and/or judgments of the epistemic status of necessary extrapolation premises. This can identify where and how individual analysts differ and provide a useful format for decision-making and conflict resolution.

An equally important role for the framework is to identify sources of uncertainty for organizing future research. It makes clear why the epistemic status was assigned a particular value. Research may then focus on critical points at which weaknesses in the reasoning process were evident. The framework also clarifies how weaknesses depend on philosophical positions, such as the assignment of intellectual obligation and the treatment of coherence. This suggests an important role for research not only into the etiology of cancer, but into the validity of philosophical positions that ultimately underlie all judgments of the rationality of claims within hazard identification.