Primary Prevention and Precaution in Hazard Identification in the NIEHS/NTP: Body in the Morgue Approach

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SYNOPSIS

In the spirit of stimulating reevaluation of the methods of public health science, this article explores the methods of cancer hazard identification at the National Toxicology Program (NTP) from the perspective of primary prevention and precaution. The NTP is a cooperative effort of three federal agencies: The National Institute of Environmental Health Sciences (NIEHS, the lead government institute); the National Institute for Occupational Health (NIOSH), in the Centers for Disease Control and Prevention; and the National Center for Toxicology Research (NCTR), in the Food and Drug Administration. NTP coordinates toxicological research and testing programs within the Department of Health and Human Services (DHHS), and through its annual Report on Carcinogens (RoC), identifies and characterizes cancer hazards—the first step in quantitative risk assessment—for the federal government. The foundation of NIEHS policies, for environmental health research, is quantitative risk assessment (QRA). The author examines the opportunities for primary prevention and precaution, and the extent to which the policies of NIEHS in general, and the NTP in particular, do and do not realize that potential. Special attention is paid to the issue of cancer hazard identification. Critical comments on the process of classifying carcinogens in the Ninth and Tenth Reports on Carcinogens are presented, based on the minutes of the Board of Scientific Counselors Subcommittee meetings.

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Under our current environmental health regime, scientists in government research and regulatory agencies must develop predictive schema to define the levels of environmental exposure that would lead to pre-determined "acceptable" levels of disease in exposed populations. U.S. environmental regulation is officially based on risk analysis and its professed scientific component, quantitative risk assessment (QRA). The National Institute of Environmental Health Sciences (NIEHS) is the government agency responsible for research on human environmental health and thus provides the scientific underpinnings that support QRA. The National Toxicological Program (NTP) was created as a cooperative effort to coordinate toxicological research and testing programs within the Department of Health and Human Services (DHHS). The lead government institute for the NTP is NIEHS; the director of the NIEHS is also the director of the NTP. The National Institute for Occupational Safety and Health (NIOSH), in the Centers for Disease Control and Prevention, and the National Center for Toxicology Research (NCTR), in the Food and Drug Administration (FDA), are the other two institutional components of NTP.[1] The NTP Executive Committee also has representatives of seven additional federal agencies: Agency for Toxic Substances and Disease Registry, Consumer Product Safety Commission, Environmental Protection Agency, Occupational Safety and Hazards Association, Department of Health and Human Services, National Institutes of Health, and National Library of Medicine. Although NIOSH, FDA, NCTR, and other federal agencies, in some way, participate in NTP discussions, the overall policy direction of the program is determined by NIEHS. This article examines the opportunities for primary prevention and precaution, and the extent to which the policies of NIEHS in general, and the NTP in particular, do and do not realize that potential. *Primary prevention* in epidemiology is defined as prevention of new cases of disease, i.e., activities that decrease disease incidence. *Secondary prevention* is defined as early detection of disease and effective medical treatment to decrease morbidity and mortality, i.e., decrease disease prevalence.[2] From an engineering point of view, *primary prevention* means activities that prevent the *possibility* of disease (inherent safety), while *secondary prevention* are activities that reduce the *probability* of disease (mitigation).[3] For further discussion on prevention definitions, see Moure-Eraso et al.[4]

Three aspects of the NIEHS/NTP policies are critically evaluated in this article:

1. Overemphasis on QRA to the detriment of preventive/precautionary research, e.g., alternatives research, eliminating/reducing exposures. The risk assessment method, as practiced in the U.S. federal scientific establishment, relies on analysis of one environmental exposure at a time to determine its "acceptable level of exposure," without any efforts to propose preventive/precautionary alternatives. The NTP Report on Carcinogens effort starts the risk assessment process with carcinogenicity hazard identification.
2. Overemphasis on identifying the genetic basis of hyper-susceptibility—despite its potential discriminatory consequences—which has little to do with primary prevention.
3. Tendencies of the NTP carcinogenic hazard identification process to reach non-precautionary decisions based on listings and classifications. This occurs because of an elaborate process consisting of a large number of internal policy reviews, whereby independent scientific and public input are diluted and provide a very limited opportunity for independent (public) participation.

NIEHS POLICIES AND RISK ASSESSMENT

Even though NIEHS recognizes that stakeholders are increasingly aware that the scientific foundation of many QRAs is weak,[5] it considers QRA to be the basis of "good science for good decisions."[6] NIEHS concentrates its research efforts to provide the scientific basis for all the stages of risk assessment: hazard identification, dose-response analysis, exposure assessment, and risk characterization.

It is the view of the NIEHS/NTP Director that the uncertainties—defined as problems of quality and completeness of information—of the risk assessment process can be addressed by three actions, or strategic investments: (*a*) to develop high-throughput technologies that could accelerate toxicity testing and generate mechanistic understanding of toxicity; (*b*) to incorporate individual susceptibility into risk assessment; and (*c*) to establish a rational basis for testing and regulatory decision-making.[7] The strategic investments of NIEHS do not include the study and prioritization of primary prevention interventions, but rather emphasize more detailed methods to characterize the risk of current environmental exposures (one substance at a time), accepting the inevitability of exposure as a given.

With regard to the study of individual susceptibility, substantial new research investments have recently been made to stimulate the use of genomics to study toxicological and environmental health problems. Five-

year grants, totaling more than $37 million, were offered in 2001 to five academic research organizations that will join with NIEHS to form a Toxicogenomics Research Consortium. This Consortium will attempt to apply genomics to understand how disease occurs, identify potential environmental hazards, predict potential disease, identify exposed individuals, and prevent disease.[8] An emphasis on identifying susceptible populations appears to be the centerpiece of this effort. The NIEHS/NTP Director recognizes that the utility of information on susceptibility to reduce environmental risk has not yet been determined. However, he envisions several possible approaches for its use:[7]

1. Screening using genetic variation;
2. Eliminating or reducing exposures;
3. Providing gene therapy to exposed populations;
4. Providing pharmacological interventions.

The only primary prevention approach in this list is number two. However, NIEHS does not invest a significant amount of intramural or extramural research resources to address exposure elimination/reduction. For the past 12 years, the lion's share of NIEHS resources has been concentrated in the approaches that emphasize secondary prevention, such as the definition of susceptible populations (molecular genetics), and mechanistic studies of uptake metabolism and excretion of environmental pollutants (molecular biology). The NIEHS/NTP Director is aware of the potential "ethical risks" implicit in projects that identify hyper-susceptible individuals, particularly individuals with environmentally associated diseases. To address any potential "ethical risks," NIEHS claims to have engaged a full-time ethicist to oversee research activities.[7] It is unclear what the NIEHS policies are concerning potential discrimination or how the NIEHS "ethicist" will address these issues. Again, all these efforts accept current environmental exposures as inevitable, rather than preventable. These exposures are to be analyzed to identify the mechanisms of toxic action at the molecular level in order to determine the acceptable level of harm for the general population and for whomever might be identified as hyper-susceptible to the exposure. There are no substantial resources invested by NIEHS in programs to eliminate or reduce these environmental exposures.

Alternatives analysis and other primary prevention/precautionary approaches, such as the precautionary principle, cleaner production, pollution prevention, sustainability, and so on,[9] are not a subject of substantial research in NIEHS (or the subject of systematic research in any other federal health agency).

One reason for NIEHS' disregard for the precautionary principle might be its views on precautionary approaches. The NIEHS/NTP Director considers the precautionary principle as simply one of the many default assumptions in the risk assessment process that needs to be overcome by the elimination of scientific uncertainties.[7] NIEHS states that the debates in risk assessment revolve around two issues: (*a*) levels of comfort with default assumptions (and the precautionary principle); and (*b*) the potential for standards to be set at needlessly low levels, which offer no added benefit in protecting health. NIEHS' assumption seems to be that the decrease of uncertainty invariably leads to a less strict standard. Dioxin is an important example where this was not the case.

NIEHS has proposed the application of the scientific knowledge generated by its Environmental Genome Project and, in the future, the new Toxicogenomics Center as the strategic, holistic approaches that will target the significant information gaps in risk assessment and eventually eliminate uncertainties.[7]

THE NATIONAL TOXICOLOGY PROGRAM AND CANCER RISK ASSESSMENT

Over the past 22 years, NTP has been studying risk assessment methodologies on a substance-by-substance basis. The NTP has developed mathematical risk assessment models, which are used for quantifying the sequence of events that starts with chemical exposure and ends with toxicity. The NTP has also produced physiologically-based pharmacokinetic models to be applied to risk assessment components (e.g., hazard identification, dose-response relationships), and also to facilitate inter-species comparison and quantification of inter-individual variation.[1]

Carcinogenicity

One of the NTP key functions is the characterization of carcinogenic substances. This activity is the hazard identification step of QRA. Since 1978, the NTP has tested more than 500 chemicals for carcinogenicity and has confirmed the cancer hazard identification of important carcinogens, including dioxin, benzene, methylene chloride, PCBs, and ozone. NTP considers the periodic publication, Report on Carcinogens (RoC), as one of its most important contributions to public health policy. The publication contains a list of substances that may pose a cancer hazard to human health. The RoCs are described as informational scientific and public health documents. To date nine cumulative reports have been published. The last edition was issued in May 2000.

The RoCs serve as meaningful compilations of: (*a*) the cancer data available for the listed substances in humans and/or animals; (*b*) the potential for exposure to these substances; and (*c*) the regulations required by federal agencies to limit exposures to these substances or exposure circumstances. The RoCs do not present risk assessments of cancer potential, but provide a clear cancer hazard identification.

The evaluation of substances listed in the RoC is performed by scientists from the NTP, other federal health research and regulatory agencies, and non-governmental institutions (see Board of Scientific Counselors RoC Subcommittee). The listings in the RoC identify a substance or exposure circumstance as a known, or reasonably anticipated, human carcinogen and also represent an initial step in hazard identification, which is generally considered the first step in risk assessment. In the view of the NTP, it is necessary to conduct a complete risk assessment in order to estimate the potential for any substance to harm human health. Complete QRAs do not appear in the RoC. It only records the cancer hazard identification and characterization by the NTP for substances or exposure circumstances listed in the RoC.

During 1994 and 1995, the criteria for listing a substance in the RoC and for de-listing a substance were revisited in a series of open public meetings. In recognition of advances in understanding the biological events involved in carcinogenesis, the criteria for listing were expanded to include a broader array of information related to the carcinogenic processes. In addition to epidemiology studies and studies to detect carcinogenic effects in experimental animals, other information contributing to scientific judgments about carcinogenicity (such as mechanistic concerns) was formally introduced into the process of deciding whether to list a chemical. Also, formal procedures for consideration of nominations to remove a substance from the listings were adopted. The revised criteria for listing a substance in the RoC were approved by the DHHS Secretary on September 13,1996. The substances newly included in or removed from the Ninth RoC were evaluated according to the criteria described below.[10]

Substances are classified in two categories:

1. *Known to be human carcinogens:* Defined as those substances for which there is sufficient evidence of carcinogenicity from human studies, which indicate a causal relationship between exposure to the agent, substance, mixture or exposure circumstance, and human cancer. Human studies are defined as human epidemiology studies and/or experimental studies of human tissues or cells. These experimental studies could include metabolic and toxicokinetic considerations as well as evidence of genetic damage, DNA binding, or persistence of DNA lesions in exposed humans.

2. *Reasonably anticipated to be human carcinogens:* This category includes those substances for which there is limited evidence of carcinogenicity in humans and/or sufficient evidence of carcinogenicity in experimental animals. Sufficient evidence in animals is demonstrated by positive carcinogenicity findings in multiple species, or at multiple tissue sites, or by multiple routes of exposure, or to an unusual degree with regard to incidence, site or type of tumor or age at onset.

   In making determinations, there may be substances for which there is less than sufficient evidence of carcinogenicity in humans or laboratory animals, but for which there are compelling data indicating that the substance could cause cancer in humans. Conversely, there may be substances for which there is evidence of carcinogenicity in laboratory animals, but also compelling data indicating that the agent acts through mechanisms that do not operate in humans and, therefore, would not reasonably be anticipated to cause cancer in humans.

   Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgments, with consideration given to all relevant information. Relevant information includes, but is not limited to dose-response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects or other data relating to mechanism of action, and/or factors that may be unique to a given substance or exposure circumstance.[10]

In 1999, NTP unilaterally, and without public discussion, added an additional "clarification" to the carcinogenicity criteria regarding information from human studies and their application to the listing of a substance determined to be a "known human carcinogen." The text of this addendum, entitled "Clarification of Criteria," was developed by NTP in April 1999 to conform the classification of "known human carcinogens" to new, narrower criteria that was previously defined in 1996. This clarification was issued in response to litigation over the listing of TCDD (dioxin) in the Ninth RoC as a "known carcinogen." (Personal communication, C.W. Jameson, Head RoC, NIEHS/

NTP, October 21, 2002.) There is an important distinction between the characterization of a substance to be a "known human carcinogen" or "reasonably anticipated to be a human carcinogen." The practical difference is that the "known" classification recognizes, without caveats, the ability of a substance to produce cancer in humans, while the "reasonable anticipated" classification only recognizes the ability of a substance to produce cancer in animals. The details and consequences of this difference and the NIEHS/NTP changes of criteria will be explored in detail below in the context of the classification of vinyl halides by the Board of Scientific Counselors (BSC) in the meeting of January 20, 2000.

NTP Report on Carcinogens listing/de-listing procedures

The NTP listing or de-listing procedure follows an exhaustive process with eight different review phases (see Table). It is remarkable that to classify a substance as a human carcinogen—either "known" or "reasonably expected to be"—requires the majority vote of federal scientists of eleven major federal research and regulatory agencies in three successive authority phases—Review Group One (RG1), Review Group Two (RG2), and the NTP Executive Committee—and a similar majority vote of the independent BSC. In addition, the NIEHS/NTP Director and the DHHS Secretary, a Cabinet position, add their own reviews, followed ultimately by the final agreement (or disagreement) of the U.S. Congress. It should be remembered that this elaborate process is only the first step—hazard identification—of the very lengthy QRA process, which is defined as objective and scientific. The investment of resources required to move a single chemical through this first step is nothing less than astonishing. The National Science Foundation has remarked on the staggering costs of the risk assessment.[11]

Table. Phases of review and procedures for listing carcinogenic substances in NTP Report on Carcinogens

Review phases	*Groups/Institutions involved*	*Actions*	*Documents produced*
1st Review	NIEHS/NTP/RoC Review Committee (RG1)	—Preparation draft report to 2nd review phase —Request public comments —Vote on listing	—Draft Background Document (BD) —Federal register announcement
2nd Review	NTP Interagency Working Group for RoC (RG2)	—Review public comments —Review draft report —Vote on listing	—Reviewed Draft BD
3rd Review	Board Scientific Counselors BSC Sub-Committee (Independent Scientific Board)	—Review edited draft of BD —Vote on listing	—Public minutes —Voting report
4th Review	Public review	—Solicitation of all public input	—Federal register announcement
5th Review	NTP Executive Committee[a]	—Review public comment and BSC listings	—Voting report
6th Review	NIEHS/NTP Director	—Decision based on evaluation of reports from previous phases	—Draft RoC to DHHS Secretary
7th Review	DHHS Secretary	—Upon approval submits RoC to Congress	—Final RoC draft
8th Review	U.S. Congress	—Upon approval release RoC —Publication trade journals	—Published RoC —Federal register announcement

[a]Agency for Toxic Substances and Disease Registry, Consumer Product Safety Commission, Environmental Protection Agency, Food and Drug Administration, National Center for Toxicology Research, The National Institute for Occupational Safety and Health, Occupational Safety and Hazards Association, Department of Health and Human Services, National Institutes of Health, National Library of Medicine, National Institute of Environmental Health Sciences, National Toxicological Program

If the federal government were to invest the resources assigned to only this first step of risk assessment to the other three QRA steps, e.g., dose-response relationships, exposure assessment, and risk characterization (which are arguably more resource and time intensive than the hazard identification), the total costs for each substance assessed would be exorbitant.

Prevention challenges and opportunities in NTP (RoC)

The classification of a substance, or process, as carcinogenic has profound public health implications. The public categorization of a substance as a "known human carcinogen" triggers public calls for actions to prevent exposure at all levels of use. A categorization as "reasonably expected to be a human carcinogen" has not traditionally triggered such a radical call, because the implication of this categorization is that there are not human data for classification as a "known human carcinogen" and therefore less strict precautions would be necessary. However, NTP is only responsible for the hazard identification step of the risk assessment. Since neither NTP nor NIEHS call for action steps to prevent exposures, other government agencies—mostly the regulatory agencies at the federal and state levels—make this call for carcinogenic substances. From the point of view of primary prevention, i.e., as embodied in the precautionary principle, it is important to avoid a Type II error (false negative), even on the categorization of a substance as a "known human carcinogen" or "reasonably expected to be a human carcinogen." Therefore, an accurate hazard identification from NTP RoC is a vital precautionary finding. Conversely, the exhaustive eight-level review process to classify the substance makes it unlikely that a Type I error (false positive) could ever occur. Thus, the NTP process protects against declaring a substance a carcinogen when it is not, but does not afford equal attention to incorrectly declaring a substance a noncarcinogen (particularly if it takes so much time and resources to study each one).

The most severe case of failure to exercise precaution takes place when a substance is improperly delisted from the NTP RoC. Less severe consequences would take place if a substance were misclassified as "reasonably expected" when it should be a "known" human carcinogen; these errors are indeed important and more easily reversible. However, the complicated process of review only permits open public discussion in two phases of the process: third review phase, BSC, and fourth review phase, public comment. These two *fora* are crucial for the classification process because they are the only place in the process where meaningful public participation by the stakeholders takes place.

Ninth RoC independent Board of Scientific Counselors debate on public health implications of NTP decisions

The deliberations of the BSC to produce the Ninth RoC were conducted under the new classification criteria approved by the DHHS Secretary in 1996 and described above. The Ninth RoC contains 218 entries, 14 of which have not appeared in earlier RoCs. This report also reclassifies 1,3-butadiene, cadmium and cadmium compounds, direct black 38, direct blue 6, ethylene oxide, and silica (crystalline, respirable size) from "reasonably anticipated to be a human carcinogen" to "known to be a human carcinogen," with corresponding revisions of the earlier entries for these chemicals. Two substances, saccharin and ethyl acrylate, have been removed from the Ninth RoC as a result of formal reviews for de-listing, while one substance methyl-tertiary-butyl ether (MTBE) was not recommended for listing.[12] There were vigorous discussions and split votes on the de-listing decisions in the BSC RoC Subcommittee.

The decision to de-list ethyl acrylate was one of the first issues to be voted on by the BSC. The split decision was based on the opinion of some counselors that the positive cancer results in the animal bioassay by gavage were not relevant to human exposures. However, an epidemiologic study of human exposure showed excess colon and rectal cancer in the exposed population. Nonetheless, the final NTP decision after the eight review phases of the Ninth RoC was that the human study, by itself, "could neither establish nor rule out a causal relationship of ethyl acrylate with cancer."[12]

A review of the saccharin listing generated another similar BSC split decision. This was based on the perception that the observed bladder tumors in animal (rat) studies occur—in the opinion of the de-listers—through mechanisms not relevant to humans. Here again, there were positive human cancer epidemiological studies but, according to NTP, the epidemiology data showed no consistent evidence that saccharin is associated with increased bladder cancer overall. However, studies did show a small increased risk in some subgroups, such as heavy users of artificial sweeteners. The NTP stated that those results "cannot be unequivocally excluded." It also stated, "With regard to the general population, if sodium saccharin is a risk factor, it is weak and *cannot be proven or disproved* due to lack of actual exposure data and intrinsic limitations of existing epidemiology studies"[12] [emphasis added].

A precautionary approach—under the constraints of these cancer hazard identification procedures—would call for these two substances to be regulated as carcinogens, given the scientific uncertainties that could not rule out casual relationships for human carcinogenicity. Proponents of the precautionary principle point out that the limitations of the currently available carcinogenicity tests, and in particular, their inability to quantify causal relationships between exposure and effect in human studies, are frequently misunderstood as evidence of safety.[13] In the case of these two substances, they were de-listed even though positive, well conducted animal experiments have shown evidence of carcinogenicity.

This type of misunderstanding is usually found among: (*a*) those that make risk *management* decisions; (*b*) scientists that make risk *assessment* decisions; and (*c*) stakeholders benefiting from the continued production or use of the toxic substance. However, having evidence that can neither prove nor disprove that a given substance is a human carcinogen is not equivalent to evidence declaring the substance safe with respect to carcinogenicity.[13]

In the case of MTBE, although there were relevant and well conducted animal cancer bioassays studies, a slim majority (6 out of 11) of the members of the BSC RoC review phase reached the conclusion that the data did not warrant listing the substance in the RoC.[12] The following phases of review agreed with the narrow BSC majority. After publication of the Ninth RoC in May 2000, this view was challenged in the scientific literature by MTBE researchers,[14] casting doubts on the scientific and public health wisdom of the BSC RoC decision. (For a full text of the BSC discussion of the issue, consult the NIEHS/NTP internet site).[12] After publication of the Ninth RoC in May 2000, this view was challenged in the scientific literature by MTBE researchers, casting doubts on the wisdom of the BSC RoC decision.[15]

Tenth RoC independent BSC debate on public health implications of NTP decisions applying the precautionary principle for vinyl halides

During the BSC RoC Subcommittee's carcinogenicity classification discussion in preparation of the Tenth RoC, the issue of public health implications of the classification scheme were addressed with respect to two substances vinyl flouride (VF) and vinyl bromide (VB).

At issue was whether to classify VF and VB as either "known human carcinogens" or "reasonably anticipated to be a human carcinogens." The criteria used to make the classification were identical to the 1996 NTP classification criteria presented above.

The first and second review phases from NIEHS/NTP (RG1) and eleven federal agencies (RG2) had recommended that the two chemicals be classified as "reasonably anticipated to be a human carcinogen."[15] However, the NIEHS/NTP presenter of the data, Dr. R. Melnick, commented that two "no" votes by RG1 pertained to the belief that VF should be a "known human carcinogen," despite the lack of human data, because the tumor profiles, the genotoxicity, metabolism, and DNA adducts formed were directly analogous to vinyl chloride (VC), a substance with reliable human carcinogenicity data (VC has been classified as a "known human carcinogen" by NTP since 1998 and by the International Agency for the Research of Cancer (IARC) from the World Health Organization since 1987).[15] With that background, the deliberations at the BSC started with presentations by primary and secondary reviewers making their classification recommendations for VF and VB. All three independent primary reviewers agreed on three points:

1. No data were available suggesting that mechanisms thought to account for tumor induction by VB and VF in experimental animals would not also operate in humans;
2. The fact that the three vinyl halides—VC, VB and VF—induced rare tumors (angiosarcomas of the liver in rats) and induced the formation of similar DNA adducts suggested a possible common mechanism of carcinogenicity for these three vinyl halides;
3. No human studies on the potential carcinogenicity of VF and VB had been reported.

Based on these considerations, one of the reviewers proposed that VB and VF, for which there were no human data, could be combined with VC, for which there *is* human cancer data, as "vinyl halides" and listed as "known to be human carcinogens."[15] However, NTP decided that this was not possible since the substances were presented separately for review and not as a group, and, most importantly, the public would not have the opportunity to be informed or offer comments.

Since this approach to classifying the two vinyl halides as "known human carcinogens" was not accepted, a second reviewer proposed that on the basis of the previous discussion—concerning the similarities with VC in mechanisms of chemical activation, chemical structure, genotoxicity, DNA reactivity, and site concordance for carcinogenic effects among these three chemicals—it seemed that the definition of "known to be a human carcinogen," provided in the criteria al-

lowed such a recommendation for VF and VB. The reviewer quoted from the criteria as follows: "Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given to all relevant information."[15] In this case, "all relevant information" showed that all three-vinyl halide congeners are genotoxic *in vivo* and *in vitro* systems, and they are metabolized to similar DNA reactive intermediates, i.e., haloethylene oxides and haloacetaldehydes. Therefore, "scientific judgment" should dictate that VF and VB, like VC, could be considered as "known human carcinogens."[15]

After a lengthy discussion, a vote was taken in which the BSC decided to recommend, by a slim margin, that both VF and VB be classified as "known human carcinogens." The dissenting members stated that they voted against this classification because, in their opinion, the lack of human data made it more appropriate for the chemical to be listed as "reasonably anticipated to be a human carcinogen."[15]

The recommendation of the BSC to the NTP Executive Committee—the fourth review phase—was to list VB and VF as "known human carcinogens." The final decision made by the NIEHS/NTP Director was to classify both VB and VF as "reasonably anticipated to be a human carcinogen," disregarding the recommendation of the BSC from the January 2000 meeting. (Personal communication, C.W. Jameson, Head RoC, NIEHS/NTP, October 21, 2002.)

NTP changes the carcinogenic criteria

In April 1999, NTP unilaterally added to their published carcinogenicity criteria a new explanatory paragraph with the title, "Clarification of Criteria." This paragraph stated: "The 'known human carcinogen' category requires evidence from studies of humans. This can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues from humans exposed to the substance in question and useful for evaluating whether a relevant cancer mechanism is operating in people."[16] This paragraph did not appear in either of the two RoC Background Documents, dated December 16–17, 1999, for vinyl bromide and vinyl flouride.[17,18] These two documents were presented to the members of the BSC as the basis for the review and reflected the 1996 NTP criteria that were to be operative during the deliberations of the BSC. As mentioned before, the clarification paragraph was not supplied to the BSC members by the NTP/NIEHS staff as their new criteria to evaluate VF and VB during the January 20–21 deliberations of the BSC RoC NTP. Although the clarification appears on the Federal Registry of April 9, 1999, it was only added to the NTP web site on February 2000, one month after the January 2000 BSC meeting, under the title, "Clarification of Criteria."[18] The original criteria, developed through extensive public hearings in 1996, were clear enough. NTP used the 1999 change on the rules of classification to amend the decision of the BSC about classifying VB and VF as a "known human carcinogen" at the fourth and higher review phases (see Table). NIEHS/NTP, by changing the criteria of classification, did in fact preempt the possibility of a final reclassification of VF and VB as "known human carcinogens."

Regardless, the BSC vote and recommendation reflects a clear application of the precautionary approach to human carcinogenicity. The original RoC 1996 listing criteria reads as follows:

> Conclusions regarding carcinogenicity in humans or experimental animals are based on scientific judgment, with consideration given *to all relevant information*. Relevant information includes, but is not limited to dose response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive sub populations, genetic effects or other data relating to mechanism of action, and/or factors that may be unique to a given substance or exposure circumstance.[10] [emphasis added]

By applying this listing criteria, the BSC was interpreting "all relevant information" to mean that VF and VB were "known human carcinogens" based on well conducted animal experiments on carcinogenicity, and evidence of human cancer effects by analogy with its homologue, VC. The chemical, molecular, cytological, and mutagenic behaviors of these two chemicals suggest a common mechanism of human carcinogenicity with VC. The BSC decided that there was no need to wait until human epidemiologic evidence of carcinogenicity was recorded for VF and VB. It was precautionary action in the absence of comprehensive information but without any doubt of its scientific validity, given the clear published biological and mechanistic analogies with VC. The message of this action was that "the body in the morgue approach" to environmental cancer would not be the only standard to establish cause for human carcinogenicity.

As it turned out, at the completion of the review, NIEHS/NTP RoC—presumably by applying their new "Clarification of Criteria," which requires human cancer fatalities—decided that VF and VB were not "known human carcinogens" but "reasonably anticipated to be a human carcinogen." (Personal communication, C.W. Jameson, Head RoC, NIEHS/NTP, October 21, 2002.) It is our contention that the NIEHS/NTP, by making this decision, was not using "all the relevant information" as required by the original 1996 criteria require-

ments. They also lost an opportunity to practice primary prevention yet again.

DISCUSSION AND CONCLUSIONS

There are opportunities for and challenges in applying the precautionary principle, and thus primary prevention, in environmental health. The current process of carcinogen identification in the NTP is tortuous and expensive; it leads one to doubt the wisdom of QRA as our main analytical environmental health tool. Given the public health consequences of carcinogen classification, it is important to engage it with a preventive outlook. At present, input by independent scientists and the public is diluted within the lengthy eight-phase internal governmental review process. And it can easily be ignored by the NTP/NIEHS. Instead, independent scientists can still contribute to the BSC RoC process by taking the precautionary approach to the classification of human carcinogens, such as VB and VF.

A fair methodological question might be: Why can't QRA begin when carcinogenicity data are available rather than waiting for the elaborated listing process of the NTP RoC?

The NTP RoC de-listing process, on the other hand, can also have serious effects on public health. By adopting a rigid reductionist approach to causality, and by ignoring conflicting results, a decision can be made to de-list a substance previously classified as a carcinogen, with potentially dire effects for exposed populations. Although a carcinogenic substance might produce tumors on specific sites through mechanisms exclusive to a non-human species (an assumption not fully validated), this does not prove that the same substance will not follow different mechanisms to produce tumors in other sites in humans. The mechanisms of carcinogenicity purported to be exclusive to non-human species may actually represent untested hypotheses in need of validation.

It is also disturbing that NIEHS has used, seemingly, arbitrary changes in their criteria for the listing of carcinogens to demand exclusively human cancer data to classify human cancers. These changes appear to contradict the previous criteria that require consideration of "all relevant information," regardless of its origin. The case of the vinyl halides amply illustrates the need to look at "all relevant information," e.g., dose-response, route of exposure, chemical structure, metabolism, pharmacokinetics, sensitive subpopulations, genetic effects or other data relating to mechanism of action, and/or factors that may be unique to a given substance or exposure circumstance.[10] The spirit of these criteria appears to be to apply all the scientific data available to provide scientific judgments that protect public health—our first priority.

In summary, the current hazard identification process for carcinogens is slow and long, and does not address the issue of alternatives. It sidesteps precaution by requiring an enormous multilevel process, which requires perfect human data before identifying a substance as "known human carcinogen," instead of favoring preventive approaches for human health or alternatives in the face of uncertainty. The current process favors the status quo by accepting human exposures until human data on cancer are generated; or in the words of Anthony Mazzocchi—union representative of oil, chemical and atomic workers—"the body in the morgue approach."

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