UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF THE ADMINISTRATOR
SCIENCE ADVISORY BOARD

EPA-SAB-EHC-92-021

September 15, 1992

Honorable William K. Reilly
Administrator
U.S. Environmental Protection Agency
401 M Street, S.W.
Washington, D.C. 20460

Subject: Science Advisory Board review of the Office of Toxic Substances draft *Formaldehyde Risk Assessment Update* document.

Dear Mr. Reilly:

In 1987, the Office of Toxic Substances examined the non-cancer and cancer effects associated with formaldehyde exposure *(Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde).*

EPA conclusions on the non-cancer effects associated with exposure to formaldehyde were based mainly upon existing reviews by the National Research Council, the Consensus Workshop on Formaldehyde, and the Interagency Risk Management Council. The major non-cancer human health effects posed by inhalation exposure to formaldehyde were attributed to the irritating nature of the chemical. There was also considerable evidence advanced for the carcinogenicity of inhaled formaldehyde in animals. EPA also reviewed 28 epidemiologic studies and concluded that "limited" evidence existed for an association between formaldehyde and human cancers. The evidence weighted most heavily for an association with cancers of the upper respiratory tract (nasopharynx, nasal cavity and sinus, and buccal cavity).

Based on limited epidemiologic evidence for an association of upper respiratory tract cancer with formaldehyde exposure, and sufficient animal evidence for an induction of nasal tumors in formaldehyde-exposed animals (along with supporting genotoxicity evidence), the EPA classified formaldehyde as a probable human carcinogen (Group B1). The epidemiologic studies were considered inadequate for quantitative risk assessment, so that the quantitative risk assessment of formaldehyde

reported in 1987 was based on rat bioassay data in which nasal squamous cell carcinoma incidence increased with increasing formaldehyde levels in both males and females.

An updated Formaldehyde Risk Assessment was presented to the Environmental Health Committee for review by the OTS on July 17, 1991. The assessment incorporated information that had become available since the release of the 1987 report on formaldehyde. The updated document reviews the evidence bearing on both the cancer and non-cancer effects of inhaled formaldehyde vapor.

The major issues identified for discussion were:

a. The weight-of-evidence support for a classification of formaldehyde in Group B1.

b. Adequacy of the evidence for the use of the nasal DPX (DNA-protein cross-links) data as a measure of intracellular dose for quantitative risk assessment.

c. Justification for not using interspecies scaling factors.

d. Support for use of the monkey, rather than the rat DPX data as dose parameters for human risk estimation.

e. Support for not using the cancer epidemiologic studies for quantitative risk assessment.

f. Adequacy of the treatment of the non-cancer effects from animal and epidemiologic studies.

The Committee found the draft *Update* to be a generally well-written document; our following comments are intended to aid in making the *Update* a more balanced, accessible,and comprehensive document.

The *Update* reaffirms the 1987 classification of formaldehyde as a Group B1 carcinogen. Animal experimental data are unequivocal, demonstrating in rats that formaldehyde is a nasal carcinogen. The epidemiological evidence is currently judged to be less certain than the experimental evidence, largely due to questions of exposure, and the Committee recognizes the basis for denoting the human evidence as "limited" and applying the BI classification. Some Committee Members noted,

however, the high relative risk estimates for nasal cancer seen in certain epidemiologic studies, and suggestions of a dose-response relationship.

As in 1987, a quantitative risk assessment was derived from the animal data. The most notable difference between the current document and the 1987 assessment lies in the increased reliance on a biomarker of formaldehyde exposure rather, than on ambient chamber concentration, as the source of dose-response information. A number of questions about this biomarker, DNA-protein cross-links (DPX), were raised by a panel of experts when its use was first proposed in 1984. Some of the questions have been resolved by results from a research program undertaken by the Chemical Industry Institute of Toxicology (CIIT). These newer data indicate that the regional concentrations of DPX serve as surrogates for formaldehyde dose to target cells. DPX data from monkeys were obtained to provide a species showing greater correspondence with human breathing patterns than do rats. The resulting upper bound inhalation unit risk (based on the linearized multistage procedure) was calculated as 2.0×10^{-3} per ppm for the rat data and 3.3×10^{-4} per ppm for the monkey data. These values are considerably lower, for both species, than the values based on airborne exposure concentrations as calculated for the 1987 document and generate several concerns, as noted below.

The Committee agrees that a risk assessment based on DPX data is a useful exercise, in that it offers a comparison between risk estimates based on environmental levels and those based on a biomarker of exposure. It also agrees that the monkey provides a model more readily extrapolated to humans than does the rat. Questions still persist, however, about the application of DPX measures to risk assessment, except as a measure of exposure. For example, the Committee shares the Agency's concerns about the absence of DPX data based on chronic exposures, and about the inability to procure information about the correlation between topographical DPX variations in the monkey and possible tumor sites.

The Committee recognizes the advances in exposure assessment stemming from DPX measures, and commends the Office of Toxic Substances (OTS) for exploring this approach. At this time, however, the use of DPX measures in quantitative risk assessment remains equivocal, except as a measure of exposure. The Committee recommends that the risk estimates based on animal DPX data be compared to those derived from the most appropriate human studies; several Committee Members suggested that the subjects followed in the American Cyanamid Corporation studies (Blair *et al*, 1986; Marsh, unpublished communication submitted to EPA's Office of Toxic Substances, 1991) might provide such a source. With estimates based on rats,

monkeys, and humans, a revised *Update* document could more cohesively compare the advantages and disadvantages of each source and model.

In addition, the Committee believes that the joint effects of particulates and formaldehyde exposure, which appear to confound the epidemiologic studies, warrant more extensive discussion. The current draft *Update* acknowledges this possibility, but, given the suggestions from the epidemiological data, devotes insufficient attention to this problem. The importance is of this issue is underlined by experimental studies of air pollutants which indicate that particulates may serve as efficient carriers for toxic materials and modify both exposure and pharmacokinetic parameters, and the fact that exposure to airborne formaldehyde typically occurs in the presence of particulates.

Non-cancer risk assessment was addressed in detail, but the Committee recommends that some issues be further expanded. These include subclinical effects, potentially sensitive subpopulations, full presentations of data, tolerance development, the contributions of particulates and exercise, and methods for the precise psychophysical measurement of irritant responses.

In summary, the Committee believes that a revised *Update* document, addressing the issues noted above, would significantly improve the Agency's ability to quantitate the risks of exposure to formaldehyde, and recommends that such a revision be undertaken.

We look forward to receiving your response to our comments.

Raymond C. Loehr

Dr. Raymond Loehr, Chairman
Science Advisory Board

Bernard Weiss

Dr. Bernard Weiss, Acting Chairman
Environmental Health Committee

ENCLOSURES

United States Environmental Protection Agency | Science Advisory Board (A-101) | EPA-SAB-EHC-92-021 September 1992

EPA AN SAB REPORT: FORMALDEHYDE RISK ASSESSMENT UPDATE

REVIEW OF THE OFFICE OF TOXIC SUBSTANCES'S DRAFT FORMALDEHYDE RISK ASSESSMENT UPDATE BY THE ENVIRONMENTAL HEALTH COMMITTEE

ABSTRACT

An updated draft formaldehyde risk assessment was presented to the Environmental Health Committee on July 17, 1991, incorporating information that had become available since the 1987 EPA report (*Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde*). The updated document reviews the evidence bearing on both the cancer and non-cancer effects of inhaled formaldehyde vapor. The Committee found the draft update to be a generally well-written document, but raised issues and provided suggestions on several aspects of the *Update*.

The current report reaffirms the 1987 classification of formaldehyde as a Group B1 (Probable Human) carcinogen. Animal data are unequivocal, demonstrating in rats that formaldehyde is a nasal carcinogen. The epidemiological evidence is currently judged to be less certain than the experimental evidence, primarily because of problems in identifying exposure. Some Committee Members noted, however, the high relative risk estimates for nasal cancer in certain epidemiologic studies and suggestions of a dose-response relationship.

As in 1987, a quantitative risk assessment was derived from animal data, but there was increased reliance on a biomarker of formaldehyde exposure (DNA-protein cross-links, or DPX) rather, than on ambient chamber concentration as the source of dose-response information. DPX data from monkeys were obtained to provide a species showing greater correspondence with human breathing patterns than do rats. The resulting upper bound inhalation unit risk (based on the linearized multistage procedure) was calculated as 2.0×10^{-3} per ppm for the rat data and 3.3×10^{-4} per ppm for the monkey data. These values are considerably lower (for both species) than the values based on airborne exposure concentrations as calculated for the 1987 document and generate a variety of questions about the application of DPX measures to risk assessment, except as a measure of exposure. The Committee is concerned (as is EPA) about the absence of DPX data based on chronic exposures, and about the inability to procure information about the correlation between topographical DPX variations in the monkey and possible tumor sites.

The Committee recognizes the advances in exposure assessment stemming from the use of DPX measures, but views their application to quantitative risk assessment, except as a measure of exposure, as equivocal. The Committee recommends that the risk estimates based on animal DPX data be compared to those derived from the most appropriate human studies, particularly on those subjects followed in the American Cyanamid Corporation studies (Blair *et al*, 1986; Marsh, unpublished communication submitted to EPA's Office of Toxic Substances, 1991).

In addition, the Committee believes that the joint effects of particulates and formaldehyde warrant more extensive discussion, since particulates may serve as

efficient carriers for toxic materials and modify both exposure and pharmacokinetic parameters. Further, the rationale for selecting the monkey model--congruency with human breathing pattern and respiratory system structure--also invokes the possible contribution of exercise because it engenders a shift toward oral breathing. Both rats (which are obligate nose breathers) and monkeys can be induced to exercise, and consequent shifts in respiration patterns could yield useful new information about the applicability of DPX.

Non-cancer risk assessment was addressed in detail, but the Committee recommends that some issues be further expanded. These include subclinical effects, potentially sensitive subpopulations, full presentations of data, tolerance development, the contributions of particulates and exercise, and methods for the precise psycho-physical measurement of irritant responses.

KEYWORDS: Formaldehyde; risk assessment; cancer; DPX.

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SCIENCE ADVISORY BOARD
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Formaldehyde Review Panel, July 17-18, 1991

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1. EXECUTIVE SUMMARY

An updated Formaldehyde Risk Assessment was presented to the Environmental Health Committee on July 17, 1991. The assessment incorporated information that had become available since the release of the 1987 EPA report on formaldehyde *(Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde)*. The updated document reviews the evidence bearing on both the cancer and non-cancer effects of inhaled formaldehyde vapor. The Committee found the draft *Update* to be a generally well-written document; our comments, as expressed in this report, are intended to aid in making the *Update* a more balanced, accessible,and comprehensive document.

The current report reaffirms the classification of formaldehyde, presented in the 1987 report, as a Group B1 (Probable Human) carcinogen. Animal experimental data are unequivocal, demonstrating in rats that formaldehyde is a nasal carcinogen. The epidemiological evidence is currently judged to be less certain than the experimental evidence. Some Committee Members noted the high relative risk estimates for nasal cancer in certain studies and suggestions of a dose-response relationship. In addition, the Committee requested that further attention be given to the analysis and interpretation of studies involving concurrent formaldehyde and particulate exposures. The Committee recognizes the basis for denoting the human evidence as "limited" and for applying the BI classification.

As was done in 1987, a quantitative risk assessment was derived from animal data. The most notable difference between the current document and the 1987 assessment lies in the increased reliance on a biomarker of formaldehyde exposure rather, than on ambient chamber concentration, as the source of dose-response information. A number of questions about this biomarker, DNA-protein cross-links (DPX), were raised by a panel of experts when its use was first proposed in 1984. Some of the questions have been resolved by results from a research program undertaken by the Chemical Industry Institute of Toxicology (CIIT). These newer data indicate that the regional concentrations of DPX serve as surrogates for acute formaldehyde dose to target cells. DPX data from monkeys were obtained to provide a species showing greater correspondence with human breathing patterns than do rats. The resulting upper bound inhalation unit risk (based on the linearized multistage procedure) was calculated as 2.0×10^{-3} per ppm for the rat data and 3.3×10^{-4} per ppm for the monkey data. These values are considerably lower, for both species, than the values based

on airborne exposure concentrations as calculated for the 1987 document and generate a variety of issues, noted as follows.

The Committee agrees that a risk assessment based on DPX data is a useful exercise, and that the monkey provides a model more readily extrapolated to humans than does the rat. Questions still persist, however, about the application of DPX measures to risk assessment, except as a measure of exposure. For example, the Committee is concerned (as is EPA) about the absence of DPX data based on chronic exposures, and about the inability to procure information about the correlation between topographical DPX variations in the monkey and possible tumor sites.

The Committee recognizes the advances in exposure assessment stemming from DPX measures, and commends the Office of Toxic Substances (OTS) for exploring this approach. At this time, however, we can not unequivocally advise for or against the use of DPX measures in quantitative risk assessment, except as a measure of exposure. The Committee recommends that the risk estimates based on animal DPX data be compared to those derived from the most appropriate human studies; several Committee Members indicated that the subjects followed in the American Cyanamid Corporation studies (Blair *et al*, 1986; Marsh, unpublished communication submitted to EPA's Office of Toxic Substances, 1991) might provide such a source. With estimates based on rats, monkeys, and humans, a revised document could more cohesively compare the advantages and disadvantages of each source and model.

In addition, the Committee believes that the joint effects of particulates and formaldehyde warrant more extensive discussion, since exposure to airborne formaldehyde typically occurs in the presence of particulates. The current draft *Update* acknowledges this possibility, but, given the suggestions from the epidemiological data, devotes insufficient attention to this problem. Its importance is underlined by experimental studies of air pollutants which indicate that particulates may serve as efficient carriers for toxic materials and modify both exposure and pharmacokinetic parameters, which for formaldehyde, would occur in the upper, rather than the lower, respiratory tract. Further, the rationale for selecting the monkey model--congruency with human breathing pattern and respiratory system structure--also invokes the possible contribution of exercise because it engenders a shift toward oral breathing. Both rats (which are obligate nose breathers) and monkeys (which are not) can be induced to

exercise, and consequent shifts in respiration patterns could yield useful new information about the applicability of DPX.

Non-cancer risk assessment was addressed in detail, but the Committee recommends that some issues be further expanded. These include subclinical effects, potentially sensitive subpopulations, full presentations of data, tolerance development, the contributions of particulates and exercise, and methods for the precise psychophysical measurement of irritant responses.

2. INTRODUCTION

2.1 Background

In an earlier document, *Assessment of Health Risks to Garment Workers and Certain Home Residents from Exposure to Formaldehyde* (EPA, 1987), the Office of Toxic Substances examined the non-cancer and cancer effects associated with formaldehyde exposure. EPA conclusions on the non-cancer effects associated with exposure to formaldehyde were based mainly upon already-existing reviews by the National Research Council (1981), Consensus Workshop on Formaldehyde (1984), and Interagency Risk Management Council (IRMC, 1984).

The major non-cancer human health effects posed by inhalation exposure to formaldehyde were attributed to the irritating nature of the chemical. These effects were sensory irritation and cellular changes. The evidence of cellular damage in humans, although limited, was considered important. A number of lower airway and pulmonary effects, including asthmatic-like responses, may occur with formaldehyde exposure. Formaldehyde-induced cellular changes in the nasal passages of rats, mice, hamsters, and monkeys were reported from a number of studies. These changes ranged from rhinitis, epithelial hyperplasia, and squamous metaplasia, to dysplasia, depending on the duration of exposure, the concentration, and the species tested.

There was also considerable evidence advanced for the carcinogenicity of inhaled formaldehyde in animals. This evidence was based on the increased incidence of a rare malignant tumor, nasal squamous cell carcinoma in two species (rats and mice), and in both sexes of two rat strains (Fischer 344 and Sprague-Dawley), in multiple inhalation experiments at high concentrations.

In 1987, EPA also reviewed 28 epidemiologic studies and concluded, based upon EPA's Guidelines for Cancer Risk Assessment (EPA, 1986), that "limited" evidence existed for an association between formaldehyde and human cancers. The "limited" classification recognizes that a credible argument for a causal association can be made, but that bias, chance, and confounding factors cannot be ruled out. The evidence weighted most heavily for an association with cancers of the upper respiratory tract (nasopharynx, nasal cavity and sinus, and buccal cavity). A lesser portion of evidence suggested that excesses in lung and brain cancers, and leukemia, may have

been associated with formaldehyde exposure in some studies. However, the biological explanation for cancers beyond the site of contact (e.g. brain cancer and leukemia) remained unclear.

Based on limited epidemiologic evidence for an association of upper respiratory tract cancer with formaldehyde exposure and sufficient animal evidence for an induction of nasal tumors in formaldehyde-exposed animals along with supporting genotoxicity evidence, the EPA classified formaldehyde as a probable human carcinogen (Group B1).

The epidemiologic studies were considered inadequate for quantitative risk assessment. Therefore, the quantitative risk assessment of formaldehyde reported in 1987 was based on rat bioassay data in which nasal squamous cell carcinoma incidence was increased with increasing formaldehyde levels in both males and females.

Casanova-Schmitz et al. (1984) proposed to use the formation of DNA-protein cross-links (DPX) as a surrogate dose for risk estimates based on animal inhalation studies. These authors developed methodology that would allow differentiation between metabolically incorporated and covalently bound formaldehyde They believed these data suggested a potential overestimate of risk at low levels of exposure.

In 1985, the Environmental Protection Agency (EPA), Consumer Product Safety Commission (CPSC) and National Toxicology Program (NTP) published their reservations to interpretations of these DPX data made by the Chemical Industry Institute of Toxicology (CIIT); these reservations were upheld by a panel of expert scientists. These (and other) critiques led CIIT to develop new methodology (Casanova et al., 1989) in order to support the existence and importance of DPX in the nasal mucosa of rats dosed with formaldehyde. The new information was responsive to the reservations raised by the Agency and it was utilized in the updated assessment brought to the Environmental Health Committee for review in 1991.

2.2. Charge To The Committee

The issues identified for discussion were:

a. Does the weight-of-evidence support a classification of formaldehyde in Group B1 (probable human carcinogen)? Is the overall epidemiologic record adequately summarized in the narrative?

b. Does the presentation on the nasal DNA-protein cross-links (DPX) as a measure of intracellular dose provide sufficient evidence to favor use of the DPX data for quantitative risk assessment?

c. Is there sufficient justification for not using interspecies scaling factors?

d. Has the preference for use of the monkey rather than the rat DPX data as dose parameters for human risk estimation been adequately explained?

e. Is there sufficient explanation of the limitations of the cancer epidemiologic studies that preclude their use in quantitative risk assessment? Has the issue of lack of concordance between risk estimates based on epidemiologic and animal data been adequately addressed?

f. Have the non-cancer effects from animal and epidemiologic studies been adequately described? Is there sufficient explanation of the limitations of the epidemiologic studies in quantitative risk assessment?

3. FINDINGS

In general, the Committee believes the direction taken by the risk assessment update will prove useful, although it will recommend numerous modifications of its content. Past SAB reviews of various agents have emphasized the desirability of incorporating as much relevant biological information as possible in risk assessments. The updated formaldehyde document takes this course by choosing to rely on a selective biomarker of exposure, DNA-protein cross-links (DPX), rather than on ambient airborne exposure levels.

3.1 Classification of Formaldehyde

The weight of the evidence is consistent with the classification of formaldehyde as a B1 (probable human) carcinogen. The animal data are unequivocal, and, moreover, the tumors are found in an unusual site and correlated with exposure markers. Formaldehyde cannot be classified as a confirmed (Category A) human carcinogen because of ambiguity in the epidemiological evidence; for example, the small number of nasal sinus cancers, which makes estimates of relative risks highly uncertain, and exposure issues, such as the possible contribution of concurrent particulate exposure. Denoting such evidence as "limited" is currently the most appropriate description. Therefore, the lower bound of uncertainty in a quantitative risk model must include zero.

3.2 Epidemiologic Data And Classification

The lack of sufficient formaldehyde exposure information, coupled with the possible confounding with simultaneous particulate exposures presents problems in using the available epidemiologic data for quantitative risk assessment. Although the Committee is uncertain about how well the epidemiologic data would support a quantitative risk assessment, we recommend that tables similar to those displayed in the 1987 document (Figure 7-1 and Table 7-5) be included. These provide estimates of the lifetime excess risk conditional on the assumption that the epidemiologic data reflect a causal association. As noted later, these calculations provide a consistency check for the estimates in the current draft based on DPX. The Tables should note that, because of uncertainty in interpretation, the lower bound for each of these estimates is zero, and the upper bound is based on the upper confidence interval for attributable risk.

Perhaps the greatest source of complications in interpretation arise from situations in which exposure occurs concurrently to particulates (wood dust, pigments) and formaldehyde. The document should describe more clearly how EPA tried to ascertain possible synergistic effects in these studies. For example, have the available studies on the association between formaldehyde in the presence of particulates and cancer been adequately considered? This is an important question because it is now clear from experimental studies of air pollutants that particulates may serve as efficient carriers for toxic materials, modifying both exposure and pharmacokinetics parameters.

Another generic question bearing on and discussed in the current report is how best to characterize exposure: Is peak exposure (what the *Update* terms dose rate) a toxicological variable independent of some measure of total (integrated) exposure? The DPX data indicate that this biomarker, derived from acute exposures, is not linearly related to exposure concentration. Do studies with other agents yield some clues? Pharmacokinetics explorations with certain organic solvents, for example, indicate that non-linearity is common. But such data, too, like the DPX data, are based largely on acute exposures.

3.3 Use of DPX Data

The use of DNA-protein cross links (DPX) as the basis for formaldehyde risk assessment is one approach designed to improve estimates of internal tissue exposure that are closer to the biologically effective dose than are measures of external concentration. Exposure levels described by chamber concentrations are universally recognized as only gross approximations to the values prevailing at biologically relevant tissues; this is one of the reasons EPA has emphasized the need for biomarkers of exposure.

Despite the progress represented by DPX measures, however, several key questions remain:

a. Although DPX are offered as a biomarker of exposure, not of carcinogenic activity, a convincing correlation between DPX concentration based on chronic exposure in an animal model, and resulting tumor incidence would strengthen its role as a relevant dose index in risk assessment. It would be important to understand the special biological or physical prop-

erties (fluid dynamics, for example) at the site of the higher tumor rates, because such understanding may help predict events occurring during human exposure.

b. Chronicity represents another conundrum. Lifetime exposures yield a nonlinear dose-response function for nasal tumors in rats. Adduct analyses for animals exposed chronically were lacking at the time of the update document. Data on the kinetics of DPX processing (formation, removal, etc.) would help clarify the validity of DPX in predicting the consequences of chronic exposures. Because DPX reach steady-state values in a relatively short time, they do not provide an index of cumulative exposure. Cell proliferation has been adduced as the intervening step. The *Update* notes, however, that the proliferative response is only a partial reflection of DPX distribution.

c. Further questions have been stimulated by data showing DPX induced, at least *in vitro*, by metal species such as chromium VI, and by agents such as methyl chloride.

d. It may prove useful to conduct an analysis based on total number of DPX, rather than their concentration in a specified area.

3.4 Interspecies Scaling Factors

In developing risk assessments, the EPA usually applies an interspecies scaling factor based upon body surface area (equating applied doses in different species as a function of $(mg/kg)^{2/3}/day$). This scaling factor is designed to reflect differences in exposure at the target organ, and differences in the rates of metabolic activation, detoxification, and other biological processes associated with toxic mechanisms.

The reasoning behind the EPA's decision not to apply its usual scaling factor is presented in the *Update* assessment document (pages 67-68). The argument for using the DPX measure in place of the surface area correction to equate delivered dose across species is valid and cogently presented. In addition, such an approach is consistent with recent initiatives on the part of the Agency to characterize inhalation exposures more precisely; they stress the site of contact rather than indirect indices such as body surface area.

The EPA document, however, does not clearly state how the scaling factor may be related to other processes involved in carcinogenesis once the carcinogen reaches the target organ. For example, the document observes that the pace of carcinogenesis is quite species dependent. For formaldehyde, tumors in the rat were observed after 18 months; in humans the latency period could extend for decades. Yet the temporal differences in DPX measures (and presumably duration of target organ exposure) between monkeys and rats were relatively modest. As for carcinogens in general, more direct measures of process are needed to account for differences in the rates of carcinogenesis between species. Because joint application of the usual interspecies scaling factor and DPX could be interpreted as a double adjustment for exposure differences across species, one alternative to a choice between the two methods might be the DPX measure and an inter-species scaling factor less than that usually applied; (e.g., the square root of the usual factor). This is suggested because the usual scaling factor is designed to compensate for differences in bioavailability and for differences in species sensitivity; the DPX scaling factor is assumed to compensate for differences in target organ dose.

3.5 Use of Monkey vs. Rat DPX

The OTS report provides an extensive discussion of the pros and cons of selecting monkey, rather than rat, DPX data as dose parameters for human risk estimation. As observed earlier, DPX concentrations may provide a more relevant exposure marker than nominal chamber concentration. The subsequent step, extrapolation to humans, evokes numerous questions about the appropriate tactics vis-a-vis selecting between rat and monkey DPX data, were they to be used for dose estimation.

The findings which support the use of the monkey-derived data are:

a. Monkeys, as primates, are anatomically and physiologically more closely related to humans; in particular, the oronasal breathing pattern of monkeys resembles that of humans. In contrast, the rat is an obligate nasal breather.

b. Available data on formaldehyde-induced tissue changes in the rat indicate that they and DPX are found only in the nasal area; in monkeys, however, DPX were observed in the nasal tissues, the trachea, and the

bronchi. Lesions were observed at the same sites, again providing a closer correspondence to locations evoking concern about human cancers. That is, rats exposed to formaldehyde (by inhalation) over an estimated lifetime showed an elevated cancer incidence only at nasal sites.

c. The anatomical sites of origin of tumors classified as lung cancer in epidemiologic studies are the bronchi, which corresponds to the binding sites in the monkey.

Objections to the arguments above have been raised, however.

a. Unlike experiments in the rat, monkey data cannot be used to explore the correlation between topographical DPX variations and tumor sites. Such experiments, for obvious reasons, are not carried out.

b The quantitative risk assessment based on DPX dosimetry in the monkey indicates a potential discrepancy with the epidemiologic data. However, epidemiology can serve as a consistency check for the risk assessments based on animal data. Most of the time, this Committee is faced with a situation in which the unit risk calculations based on animal data embody a rather conservative value compared to available human data. With formaldehyde, estimates based on animal experiments predict fewer cancers than those observed in human studies. Furthermore, nasopharyngeal and sino-nasal cancers are relatively rare in the general population compared to lung cancer, so that risk figures can be swayed significantly by even a single case. Given this unease, even if it arises from disputed interpretations of the human data, the update document should recognize its source. The document should then explicitly respond by, for example, indicating how different formulations of a DPX model might be modified to approximate the epidemiologic findings were the latter assumed as valid. Would it be feasible to try to model, given what is known about particle deposition in the respiratory tract, how particulates such as wood dust, carrying formaldehyde, (cf., Brain and Valberg, 1979) might modify DPX distribution and formaldehyde carcinogenicity? Such an exercise would provide a useful focus to the current debate.

c. Acute exposure models, as noted earlier, may not be relevant to chronic exposures. The total pharmacokinetics evaluation, for which DPX is the first entry, might be modified significantly with extended exposure, as noted in the *Update*. Because chronic exposures are the source of concern about carcinogenic potential, the update document should discuss more extensively, under a specific heading, the full implications of this problem. The document's treatment of this problem now appears in a number of scattered comments.

On balance, despite the reservations above, the Committee tends to agree with the arguments favoring the monkey DPX data rather than those of the rat. The update, however, should make certain that readers appreciate the uncertainties involved in the unit risk calculations, and that they recognize that DPX serve as a measure of exposure rather than as an index of carcinogenesis. The aim of using the monkey to model human exposure is to characterize, in essence, the effect on DPX of specified ambient formaldehyde levels so that the risk estimates, derived from standard models such as the linearized multistage, can be based on a more direct measure of dose.

3.6 Use of Epidemiologic/Animal Data For Cancer Risk Assessment

The draft OTS *Update* document does not provide sufficient explanation and discussion of why the limitations of the available cancer epidemiologic studies should preclude their use in quantitative risk assessment, nor does it adequately address the concordance, or lack of concordance, between the epidemiologic and animal data, as noted earlier. The Committee recognizes that much of this discussion is contained in the 1987 document. Many readers, however, will come to the *Update* document without access to the previous review. Committee members themselves, and even EPA staff, have experienced difficulties in obtaining earlier documents on various topics because of restrictions on archiving Agency reports. The update needs to be a more complete document and to include the more extensive analyses contained in the 1987 report.

As outlined there, and in the *Update*, the epidemiologic information available to date is based on relatively small numbers of sino-nasal or naso-pharyngeal cancers. As a result there is considerable uncertainty as to whether the excesses seen reflect a causal association with exposure to formaldehyde. In addition, although some studies

show an excess of lung cancer (a more common cancer), any excess reported reflects a weak relative risk. Under these circumstances, considerable uncertainty in the interpretation of epidemiologic studies is certain to persist. A further complication, alluded to earlier, is the possible confounding of joint formaldehyde and particulate exposure, a situation especially prevalent in certain occupational settings, but also characteristic of home environments, some of which may even exceed occupational levels. Such confounding may be multiplied by the possible contribution of exercise, perhaps more likely in occupational settings, and its influence on breathing patterns and dose parameters. Enhanced oral breathing, a consequence of exercise, elevates the dose to the lung and probably shifts relative DPX distribution. The monkey DPX model could be modified by studying exercising animals to yield such information.

In summary, the epidemiologic data should be utilized, at a minimum, as a consistency check in any assessment of the risks of exposure to formaldehyde based on animal data, perhaps by comparison with the 1987 calculations. And, even if EPA now concludes that a quantitative risk assessment is simply not feasible with the current human data, an overall point estimate can be made (with the accompanying wide bounds of uncertainty). The significance of the large difference between estimates based on animal and epidemiologic data is softened considerably by the uncertainty attached to the latter, the possibility of modification by simultaneous exposure to particulates, and by the uncertainties attached to the carcinogenic significance of the DPX measures themselves.

3.7 Use of Epidemiologic/Animal Data For Non-Cancer Risk Assessment

The Committee reviewed the OTS document and identified several concerns with the section on non-cancer effects.

Evaluation of the update led to the recommendation that the section on non-cancer risk assessment be revised, taking the following issues into consideration:

a. The current discussion treats non-cancer effects as if they were health endpoints, but subsequently minimizes the importance of some of them. Acute respiratory symptoms (e.g., irritation) and chronic respiratory symptoms (e.g., cough, wheeze) affect quality of life, and, in addition, may be indicators of developing disease. Moreover, abnormal values (for example in FEV_1) may be indicators of disease risk without being

defined as conventional evidence of disease. The document's discussion of these issues, however, implies that they are of little importance because they are not sufficiently aberrant to be considered clinically significant. **The Committee recommends that the document be revised so that the potential importance of these effects is discussed more broadly, and cogently.** EPA's position on hazardous air pollutants stands in contrast to the current evaluation.

b. A related concern is that the current discussion emphasizes mean values. As a practical result of study design and analysis in available published reports, the assessment is based largely on studies of working populations, medical students, and controlled exposures with healthy adults. This makes examination of variability in these largely young and healthy study groups all the more important in estimating exposure effects for members of more sensitive sub-populations. Extreme responses in such populations, noted in other contexts, may yield clues to the response of particularly susceptible populations. **The Committee recommends that additional information on population variability in responsiveness be added.**

c. Most of the presentation of non-cancer effects does not include display of the actual results from the studies, but rather only whether the results were (statistically) significantly different. This practice has two problems. First, it places undue importance on statistical testing without addressing (1) the preponderance of the evidence, (2) consistency across studies, and (3) indications of trends. Second, it does not provide the reader with adequate detail, even at the level of a summary of findings. **The Committee recommends that additional information addressing this concern be added. In addition, the health implications of tolerance to the irritant effects of formaldehyde should be addressed.** Tolerance is not an index of risk reduction.

d. The summary of the data in each of the sub-sections in section 6.2 is too discursive. There is no attempt to present the strengths and weaknesses of the study designs, population sizes, outcome measures, and data analyses. **We recommend that additional data be added to address this concern and that the studies before 1987 should be included as**

well, because, as noted previously, the earlier document may be unavailable to many readers.

e. At least one of the Alexandersson studies (1989) is prospective and not identified as such. The benefits of this approach in this study should be incorporated in the evaluation of pulmonary function.,

f. One problem is the focus on effects uniquely attributable to formaldehyde. Concurrent exposure to other agents, such as particulates, frequently occurs in almost any occupational study. Ignoring the effects of formaldehyde in the presence of particulates addresses an unrealistic circumstance. Only in an exposure chamber will formaldehyde exposures be free of particulates. In the general environment (indoor or outdoor) particulates will accompany any exposure. **The Committee recommends further attempts to interpret study results in terms of the independent and combined effects of formaldehyde and particulates, rather than to treat particulate exposure simply as a "confounder." Moreover, as noted in Section 3.6, the additional contribution of exercise, and how it modifies both dose and breathing pattern, needs to be considered.**

g. There is a lack of consistency between the discussion of detailed exposure estimates as they relate to non-cancer effects, and the parallel discussion related to cancer effects. Much more detailed exposure data are available for non-cancer effects. The discussion of the overall evidence suggests that no epidemiologic study could ever provide enough exposure-effect information to "precisely quantify general population risks for eye and upper respiratory effects...". This is too conservative a reading of the existing data.

h. The scientific community would benefit if this risk assessment were to identify issues needing investigation. One particular concern is the very minimal attention placed, as yet, on the use of psychophysical measures of irritant responses. The only report attempting to apply modern measures of subjective response is that of Horvath, et al., 1988 (cited in document). **This lack of attention to an important research tool**

should be noted and the Committee recommends that a section be added listing research needs.

i. The exposure descriptions for both the animal and human epidemiologic studies should be discussed in sufficient detail to enable the reader to evaluate better the data and their applicability for risk assessment.

j. The explanation of both the advantages and the limitations of the epidemiologic studies for quantitative risk assessment needs to be expanded, both in the text and in the executive summary. The reasons why the studies may not show an effect when one may exist and why the studies may be showing an effect that may not be related to formaldehyde need to be expanded. Furthermore, it is important to estimate the relative likelihood that findings from the epidemiologic studies are misleading. The executive summary also needs a brief statement qualifying the findings. The previous paragraphs suggest specific items that need to be added.

4. FINDINGS AND RECOMMENDATIONS

It is difficult to read the current document which updates the 1987 risk assessment without a summary of the documentation available at that time. An evaluation of the literature for both cancer and non-cancer effects, and how they relate to the respective risk assessment, cannot be made from the June, 1991 *Update* document alone. A careful summary of the earlier findings would be a useful and important addition to the Final Draft risk assessment. **The Committee recommends that such a summary be added.**

The current document proposes the classification of formaldehyde, as did the 1987 report, as a Group BI (Probable Human) carcinogen. The primary evidence for human carcinogenicity, the reported association between cancers of the nasopharynx and buccal cavity and formaldehyde exposure, is frequently complicated by simultaneous exposure to particulate matter. **The Committee agrees that the human evidence is "limited" and supports the BI classification.**

The current update places considerable emphasis on the use of a biomarker of formaldehyde exposure, DPX, rather than on ambient chamber concentration as the source of dose-response information. A number of questions about this biomarker, DNA-protein cross-links (DPX), were raised by a panel of experts when it was first proposed in 1984. A program to resolve these reservations was subsequently undertaken by the Chemical Industry Institute of Toxicology (CIIT), and has met most of them to the satisfaction of EPA. These newer data indicate that regional concentrations of DPX may be able to serve as surrogates for formaldehyde dose to target cells. In addition, because rats are obligate nose-breathers, DPX data from monkeys were obtained to provide comparisons with species showing greater correspondence with human breathing patterns. The upper bound inhalation unit risk based on the linearized multistage procedure was calculated as 2.8×10^{-3} per ppm for the rat and 3.3×10^{-4} per ppm for the monkey. These values,in the case of both species, are much lower than the values based on airborne exposure concentrations as calculated for the 1987 document.

The Committee views a risk assessment based on DPX data as a useful comparison with risk estimates based on environmental concentration and with the epidemiological data; for this purpose, the monkey provides a more suitable model than the rat. The Committee is concerned,as is EPA, about the absence

of DPX data for chronic exposures, and about the inability to obtain information about the correlation between topographical DPX variations in the monkey and possible tumor sites.

The Committee recognizes the advances in exposure assessment stemming from DPX measures, and commends the OTS for pursuing this course. At this time, however, we can not provide an unequivocal answer to item (b) of the Charge, namely the use of DPX data for quantitative risk assessment. There are simply too many issues as yet unresolved, to offer a definitive recommendation. This position is based on the following observations:

a. The presence of DPX may be taken as an index of acute formaldehyde exposure. In the rat, the relationship between formaldehyde concentration and DPX shows a clear non-linearity. Whether the form of this relationship will persist during chronic exposure conditions remains to be settled.

b. Definitive information demonstrating that DPX are relevant to carcinogenesis is not available.

c. Under these circumstances, DPX continue to serve as a useful intermediate step pending further explorations of chronic exposures and their connection to carcinogenesis.

We recommend that the OTS continue to pursue this issue, and suggest comparing risk estimates based on DPX data to those derived from the most appropriate human studies; several Committee Members indicated that the subjects followed in the American Cyanamid Corporation studies might contribute important new epidemiological information. With estimates based on rats, monkeys, and humans, a revised assessment document could more cohesively compare the advantages and disadvantages of each source and model. The Committee is aware of the assumptions about exposure and other variables required of such a treatment of the human data, but believes that the resulting document will attain more cogency by such an effort.

In addition, the Committee believes that the joint effects of particulates and formaldehyde warrant more extensive discussion, since exposure to airborne formalde-

hyde typically occurs in the presence of particulates. The current draft update acknowledges the possibility of interactions, but, given the suggestions from the epidemiological data, inadequate attention is directed to possible joint effects. Particulates are so ubiquitous that a "pure" formaldehyde exposure situation may be impossible to find in humans. The importance of joint effects is reinforced by experimental studies of air pollutants that demonstrate particulates may serve as efficient carriers for toxic materials, modifying both exposure and pharmacokinetic parameters. In the case of formaldehyde, the upper, rather than the lower, respiratory tract would be the source of concern. Further, the rationale for selecting the monkey model--congruency with human breathing pattern and respiratory system structure--also should invoke the possible contribution of exercise because it engenders a shift toward oral breathing. Both rats and monkeys can be induced to exercise, and consequent shifts in respiration patterns could yield useful new information about the applicability of DPX.

While acknowledging that the state-of-the-art is a rapidly moving target, the Committee nevertheless advocates that future revisions of the document incorporate the latest information. In particular, the updated Cyanamid analyses (currently unpublished update of the Blair, et al. 1986 study by Marsh, 1991), recent work on airflow patterns in rat and monkey nasal passages (Morgan et al., 1991), exercise effects on dose and dose distribution (Kleinman and Mautz, 1991), and on occupational risk factors for sinonasal cancer in woodworkers (Luce et al., 1992).

Non-cancer risk assessment was addressed in detail by the *Update*, but the Committee recommends that some issues be further expanded. These include subclinical effects, potentially sensitive subpopulations, full presentations of data, tolerance development, the contributions of particulates and exercise, and methods for the precise measurement of irritant responses.

In closing, the Committee recommends that the Agency revise the *Update* to address the issues noted above. These revisions would enhance significantly EPA's ability to quantitate the risks of exposure to formaldehyde.

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