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

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Data Available to the Administrator Concerning Formaldehyde and di(2-ethylhexyl) Phthalate (DEHP)

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TO: Anne M. Gorsuch
The Administrator (A-100)

THRU: John W. Hernandez, Ph.D.
Deputy Administrator (A-101)

Summary

At your direction I have reviewed the materials prepared by the Office of Toxic Substances in regard to formaldehyde and DEHP. I have also reviewed the materials prepared early in 1981 by OTS which were appended to a letter from NRDC, dated September 4, 1981. This memorandum is a statement of my professional conclusions and policy recommendations regarding the documents reviewed. In summary: I find that I concur with the current recommendations of OTS that formaldehyde and DEHP ought not be considered under section 4(f) and that the preliminary drafts relied on by NRDC in their letter to you were incomplete and flawed.

Technical and Policy Issues Related to Section 4(f)

The Toxic Substances Control Act (TSCA) was enacted by Congress to protect human beings and the environment from those chemical substances and mixtures whose manufacture, processing, distribution in commerce, use, or disposal pose unreasonable risks of injury. One of the provisions of the Act is Section 4(f), which states that:

> Upon receipt of 1) any test data required to be submitted under this Act, or 2) any other information available to the Administrator, which indicates to the Administrator that there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant

> risk of serious or widespread harm to human beings from cancer, gene mutations, or birth defects, the Administrator shall, within the 180-day period beginning on the date of the receipt of such data or information, initiate appropriate action under section 5, 6, or 7 to prevent or reduce to a sufficient extent such risk or publish in the FEDERAL REGISTER a finding that such risk is not unreasonable. For good cause shown the Administrator may extend such period for an additional period of not more than 90 days. The Administrator shall publish in the FEDERAL REGISTER notice of any such extension and the reasons therefor.

The purpose of section 4(f) is to identify certain chemical substances or mixtures as high priority candidates for regulatory action and establish a deadline for acting to regulate such substances as are found to meet section 4(f) criteria. A chemical could meet the section 4(f) criteria when there may be a reasonable basis to conclude that it presents a risk from one of three effects--cancer, gene mutations or birth defects, and that the risk of this effect is significant and either serious or widespread. None of these terms--significant, serious or widespread--is precisely defined in TSCA.

The common technical use of these terms in the bio-medical sciences would suggest that "significant" would address both the probability that a risk of any magnitude could occur as well as the magnitude of the risk; and that "serious" and "widespread" would address the nature (i.e., major vs. minor) of any harm resulting and the size of the affected population, respectively.

For purposes of illustration, the following examples of usage are possible:

"Significant" -

> A particular animal cancer bio-assay indicates that chemical compound X is a carcinogen in at least two species tested and all sexes in these species. Compound X generally may present a risk of being a human carcinogen. To be "significant" it should further be established that--at <u>human</u> exposure levels--the risk is probable and would be high. A different chemical, compound Y, is positive in one species, one sex and at one high dose. It could, in theory, be a human carcinogen but it need not generally be considered to pose a "significant" risk to humans based solely on the <u>one</u> positive finding. Strong evidence for human risk should generally require that the carcinogenic effect be established as active in more than one species or at more than one dose.

If for compound X above, it were found that the carcinogenic effect is due to activation of a metabolic pathway not found in humans, then the risk from compound X could be deemed not "significant" as it would not occur in humans.

The carcinogenic effects of compound X could also be found to be secondary to physiological events (deposition of microcallculi, hormonal changes, necrosis, etc.) triggered by compound X at levels used in bio-assays but not at levels to which humans are exposed. Compound X would probably not pose a "significant" risk to humans. (See footnote 1)

"Serious" -

The concept of "serious" harm would have more utility in the consideration of gene mutational events or birth defects than in the case of cancer since malignant neoplasms in general are serious. Section 4(f) also draws a distinction between benign and malignant growths by use of the term "cancer" rather than "tumors".

"Widespread" -

A teratogen could produce a minor anomaly. If this occurred at one in one hundred thousand births, it need not be necessarily "serious" or "widespread". The same outcome at one in one hundred births, however, would certainly be "widespread".

The determination that a chemical meets the criteria of section 4(f) is, by statute, made by the Administrator of EPA.

When a chemical meets the criteria for section 4(f) priority status, the Agency must decide quickly whether to initiate action. The provision states that the Administrator must, within 180 days of the Administrator's receipt of the information

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(1) These considerations as to weight of evidence to establish human risk generally follow the recognized International Agency for Research on Cancer (IARC) criteria (IARC, Internal Technical Report No. 78/003) as to whether evidence is negative, limited, or sufficient for human carcinogenicity as well as the amplification of these criteria presented by Griesemer and Cueto (Scientific Publication No. 27, IARC, Lyon; p. 259-281 (1980)). The second paragraph draws from Weisburger and Williams (in Toxicology, Casarett and Doull, Eds., 2nd edition, MacMillan, N. Y. (1981) as well as from a more recent paper of Squire (Science, 214; 877-880 (1981)).

indicating the risk, initiate appropriate action under section 5, 6, or 7 of TSCA, or explain in the FEDERAL REGISTER why the risk is not unreasonable. As a purely technical matter, only rarely would a single study provide a reasonable basis to conclude that a chemical presented or would present a significant human risk. Risk is a function of toxicity and exposure. Therefore, exposure evaluations (which generally must rely on other studies than those raising toxicological concerns) are required in order to properly quantitate risk. The probability that risk would indeed occur can in general, likewise, only be assessed by review of all the available literature on a given chemical. Only when the diverse pieces of information which must go into a proper risk assessment are assembled into a reasoned evaluation can there generally be any scientific basis on which to draw reasonable conclusions as to the nature of human risk posed by a given chemical.

In certain instances the available data on a chemical may suggest that it poses a human risk but be insufficient to reasonably support a conclusion that the chemical presents a significant risk of serious or widespread harm [i.e., similar to a section 4(f) determination] and/or an unreasonable risk [a determination called for in other parts of TSCA]. The distinction between chemicals which may pose a human risk and those which pose either a significant and/or unreasonable risk [applicable to section 4(f) and/or section 5, 6, or 7, respectively] is important from a policy standpoint. This distinction and the TSCA data collection authorities allow the Agency to deal with chemicals on which the data are suggestive but inconclusive by use of sections 4(a), 5(e), and/or 8 so as to better develop a data base. This distinction also allows the Agency to place less priority on such substances as may be found to pose less than significant human risk even though the Agency may want to retain some oversight of activities involving such a substance.

Applicability of TSCA Section 4(f):

The principle decision before the Administrator at present is whether or not the data available on formaldehyde meet the criteria set out in section 4(f) of TSCA. The technical and policy arguments that these criteria are not met are presented for each substance in this report in greater detail below. Legal conclusions as to section 4(f) are not within my realm of expertise. In this report I have tried to define the technical practicalities of section 4(f) and to address the relevant policy issues.

Generally, the approach to section 4(f) that is presented is that, until the Administrator has reviewed the available data and reached a conclusion as to the significance of risk, any designation of data as having triggered section 4(f) is

scientifically arbitrary. This has tremendous practical and scientific underpinings as, in general, no one study by itself will be sufficient to indicate "significant" risk and the required determination that "there may be a reasonable basis to conclude that a chemical substance or mixture presents or will present a significant risk . . . " should, therefore, require a synthesis of existing and newly developed knowledge. Only when this synthesis is accomplished can a reasoned conclusion, in general, be reached.

As a policy matter, it is recommended that risk situations which are "significant" in the context of priority setting via section 4(f) be clearly distinct from risk situations which are generally not of immediate regulatory interest. In terms of individual lifetime cancer risks, the various federal agencies do not tend to regulate risks of 1×10^{-5} or lower and tend to be ambivalent about risks between 1×10^{-4} - 1×10^{-5}. Certainly (as absolute risks) these risk levels could never be detected any normal way and would (using 1×10^{-4} as an upper bound) represent increments of 0.03% or less above the estimated individual risk of persons in the U.S. population as a whole. (This risk is 1 in 3 or 3.3×10^{-1} according to the most recent National Cancer Institute figures.) In OPTS the relative risk range of 1×10^{-4} to 1×10^{-6} or lower has been a low concern range in general. The use of a range is appropriate since these risks, even at the 95% upper confidence limit, are only relative estimates for specific chemicals. To use such risk estimates as absolutes is inappropriate. This point was recently emphasized by Dr. David Rall, Director of the National Toxicology Program, in testimony before Rep. Gore during the 1981 NTP appropriations hearings.

FORMALDEHYDE:

Summary

Technical and policy discussion of these points is to be found in the body of this report.

Conclusions With Respect to Formaldehyde:

I concur with the recommendations of OTS staff that formaldehyde does not meet the criteria of section 4(f) for the following reasons:

(A) There is suggestive evidence that there may be human exposure situations--based on the integrated animal data base--which may not present carcinogenic risk which is of significance.

(B) There is a limited but suggestive epidemiological base which supports the notion that any human problems with formaldehyde carcinogenicity may be of low incidence or undetectable. It would not appear reasonable to say that a significant risk situation exists from these data.

(C) Assuming that risk--of some magnitude--does exist the calculated relative risks tend to fall into ranges which normally are of from low priority to no concern such as those discussed in the section immediately above on the applicability of TSCA section 4(f).

(D) One can, therefore (and as amplified below) conclude on the basis of available toxicological data, exposure information, and risk analysis techniques that: (a) formaldehyde is a carcinogen in the rat by the inhalation route; (b) its carcinogenic potential appears to vary significantly with species and route; (c) under certain exposure conditions it could present some carcinogenic risk to humans; and (d) given available data the risk estimates suggest that certain populations may experience a carcinogenic risk--albeit low--due to formaldehyde exposure. However, because of the nature of the toxicology data and the unreliability in the exposure data one cannot reasonably conclude, at this time, that formaldehyde poses a significant risk among the U.S. population.

Interpretation of Animal Studies with Respect to Human Risk -- Of a variety of bioassays (Table I) done since 1954 to assess the carcinogenic potential of formaldehyde only two have given clear positive results attributable to formaldehyde: a Chemical Industry Institute of Toxicology Study (CIIT) reported in preliminary form by Swenberg et al, Cancer Research, 40, 3398 (1980) and a study underway at the New York University Medical Center which is an extension of an earlier New York University study of 1979. Both of these have been inhalation studies in the rat. The CIIT study used three dose levels plus a control, the New York University study used a single high dose equivalent to the highest CIIT dose. Only nasal carcinomas were found in either study. Approximate mean lifetime incidences were 0% in control rats; 0% in rats at 2.1 ppm formaldehyde; 1.9% in rats at 5.6 ppm (not statistically significant); and 50% in rats at 14.1 ppm in the Swenberg study. The New York University study indicates (by letter of August 17, 1981 from Dr. Arthur Upton) an incidence of about 10% in rats at 14 ppm of formaldehyde.

Table I: Studies Considered in Evaluating the Carcinogenic Potential of Formaldehyde

Species	Route	Dose	Length	% Incidence	Reference
Rat, ♀ & ♂, Fischer 344	inhal.	0, ppm 2.1 ppm 5.6 ppm 14.1 ppm	24 mos.	(0%) (0%) (1.9%) (50%)	CIIT study of Swenberg et al, nasal tumors only
Rat, ♂ Sprague-Dawley	inhal.	14 ppm	lifetime (19 mos. completed)	(~10%) nasal tumors	On going NYU study reported by Upton letter of Aug. 17, 1981
Rat, ♂, Sprague-Dawley	inhal.	14 ppm+ 10 ppm HCl	lifetime (27 mos.)	(27%) nasal tumors	NYU study of Laskin et al
Mouse, ♂ + ♀, $B6C3F_1$	inhal.	0 ppm 2.1 ppm 5.6 ppm 14.1 ppm	24 mos.	- (0%) - (0%) - (0%) (2%)	CIIT study of Swenberg et al, nasal tumors only
Hamster, ♂ Syrian	inhal.	10 ppm 30 ppm	lifetime	- (0%) - (0%)	Nettesheim, NCI - DOE study, 1977
Rat	s.c.[a]	formalin, 0.4%, 1 ml per animal weekly	15 mos.	(40%)	Watanabe et al, Gann, 45, 451 (1954) sarcomas at injection site only.
Rat	s.c.	HMT,[b] 40%. 2 ml per animal per week	until tumor development	(40%)	Watanabe et al, gann, 46, 365 1955 sarcomas at injection site.
Rat, ♂ + ♀ BD	oral gavage	HMT, 0.4 g/day	12 mos.	(0%)	Brendel, Drug Res., 14, 51 (1964)
Mice (CTM, SWR, and C3Hf) and Rat (Wistar)	drinking water	HMT, 2.5 g/Kg/d "	1 yr 2 yr	(0%) (0%)	Della Porte et al, Food Cosmetic Tox., 6, 707 (1968)[c]

Table I (continued)

Notes to Table:

a - sc = subcutaneous injection

b - HMT = hexamethylene tetramine

which decomposes in aqeous solution to give formaldehyde and ammonia with the stoichiometry:

$$1\ \text{HMT} \rightleftharpoons 4\ NH_3 + 6\ CH_2O$$

One gram of HMT is equivalent to 1.3 gram of free formaldehyde.

c - Della Porte et al, Tumori, 56, 325 (1970) also report a 3 generation study on Wistar rats with 2% HMT in drinking water which was negative for all three generations. This level of HMT is equivalent to about 2.5 g/Kg/d of ingested HMT which would be 3.3 g/Kg/d of formaldehyde.

The two studies used different strains of rat but are in general agreement. The CIIT study also exposed mice to formaldehyde gas but no statistically significant increase in tumors was observed. (See footnote 2.)

Other studies (some in other species and/or by other routes) have been generally negative save for a rat study of 1954 (expanded in 1955) using a subcutaneous injection route for 0.4% formalin or up to 40% hexamethylene tetramine (HMT, which gives rise to free formaldehyde, 1 gram HMT = 1.3 gram formaldehyde). In this study only sarcomas at the site of injection were found and these studies are not, therefore, generally accepted as being other than suggestive evidence of carcinogenecity. Significantly, the oral administration of hexamethylene tetramine to rats at up to 12.5 g/Kg/week was found to produce no tumors in three different investigations of up to two years duration (the same length as the CIIT inhalation study) conducted in 1964, 1968, and 1970. The oral route studies are somewhat limited by small sample sizes but, taking all three studies in aggregate, there is evidence which suggests a lack of a carcinogenic effect by this route. An important observation is that inhalation by hamsters at similar or higher exposure levels than used in the CIIT study has given a negative result. Formaldehyde appears, therefore, to exhibit considerable species specificity with the rat, the most sensitive of species so far tested.

Concern that formaldehyde gas may induce tumors in humans should be tempered by this observation that formaldehyde carcinogenicity appears to have a high degree of species specificity and a strong dependence on route of exposure. The rat, an obligatory nose breather, appears to have a particular nasal sensitivity to the deleterious effects of formaldehyde which may not be generally shared by other animals (man is not an obligate nose breather) or body sites. Based on the animal experimentation data, the most reasonable interpretation is that formaldehyde has carcinogenic potential, is probably locally acting, and is capable of both initiation and promotion.

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(2) The statistical significance of the CIIT results at 5.6 ppm in the rat (1.9% incidence observed) and 14 ppm in the mouse (2% incidence observed) was determined by CIIT as described in the CIIT document "Data Released to the International Agency for Research on Cancer (IARC) Working Group", dated October 19, 1981, which is appended as Appendix A.

The results of the CIIT bioassay are, however, sufficient to establish that formaldehyde is a potential animal carcinogen with mode and degree of exposure quite important to the toxic outcome. Based on the observed differences in response shown by rats, mice, and hamsters, different species have differing sensitivities. This may be a quantitative rather than a qualitative difference but the negative results of inhalation studies with Syrian hamsters at up to 30 ppm formaldehyde suggest that there may be qualitative differences in response among species as well. It can, however, be prudently expected that under appropriate conditions of exposure formaldehyde gas may pose a cancer risk to the respiratory tract of humans (i.e.: nasal and buccal cavities, trachea, bronchial trees, and lungs, see footnote 3). In the CIIT bioassay (see Appendix A), the development of nasal carcinomas was always preceded by hyperplasia, metaplasia and overt signs of cytotoxicity to the nasal mucosa (simply put, the animals developed open sores in their nasal tissues after which tumors appeared). In other cases, with other chemicals, where tumors appear to be secondary to cytotoxicity, no observable effect levels of exposure have been postulated (see, for example, Weisburger, J. H. and Williams, G. M. in Casarett and Doull's Toxicology, 2nd ed., MacMillan, NY (1981)). Since formaldehyde has genotoxic properties, any simple analysis is complicated but the findings of the CIIT research team which supported the bioassay have bearing on the interpretation of the results of the bioassay:

(1) At low exposure levels or short exposure times the hyperplastic and metaplastic effects of formaldehyde exposure were reversible. This suggests that a higher exposure level or longer exposure time may produce a qualitatively different outcome with respect to carcinogenesis than would result from low level or short term exposure.

(2) Normal endogenous tissue levels of formaldehyde produced by metabolism range from 3-12 Ng/g tissue (3-12 ppm). Much of this appears to be bound up as adducts to glutathione, tetrahydrofolate, and proteins. From 10%-40% of the total tissue formaldehyde appears to exist as free formaldehyde (0.3 Ng/g - 4.8 Ng/g). A sustained exposure of 3 ppm formaldehyde in air is needed to double the endogenous level of formaldehyde.

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(3) Other body sites are theoretically possible targets but, due to a variety of studies demonstrating rapid metabolic conversion of formaldehyde at or near the sites of uptake (Maloney, 6, et al; Arch. Exp. Pharmacol., 250; 419-436 (1965); McMartin, K.E., Biochem. Pharmacol., 28; 645-649 (1979)) it is expected that the respiratory tract will be the principal, possibly sole, target organ at risk. A high degree of site concordance between humans and animals has been suggested by Tomatis (L. Tomatis et al, Cancer Research, 38; 877 (1978)).

(3) There appears to be an absence of cytotoxic effects of formaldehyde at or below 1.0 ppm in air.

(4) Radio-isotope tracer measurements indicate that absorption of formaldehyde gas from imspired air is essentially complete within the nasal cavities and formaldehyde gas does not reach the trachea, bronchi or lungs of rats at the exposures used in the CIIT study.

(5) Formaldehyde is a mutagen. As such it is a potential genetoxic carcinogen. Aldehydes, as a chemical class, are also promoters of carcinogenesis (Slaga, T. J., Sivak, A.; and Boutwell, R. K.; Mechanisms of Tumor Promotion and Cocarcinogenesis, Raven Press, NY, 1978). Formaldehyde can, then, potentially both initiate and promote the carcinogenic process. A promoting and/or cocarcinogenic effect of formaldehyde is supported by other studies cited in Table I, in particular the various New York University studies. Promotion generally requires repeated, long term exposure to the promoter and is reversible [(Weisburger, J. H. and Williams, G. M.; "Chemical Carcinogenesis" in Holland, J. F. and Frei, E. (eds): Cancer Medicine, 2nd ed., Lea and Febiger, Philadelphia, 1980)], may involve damage to cellular components (Slaga et al (supra), 1978), and is a requisite, at some point, to the carcinogenic process. When taken together with the observations reported by CIIT on the reversibility of hyperplastic and metaplastic effects (vide (1) supra) and an apparent cytotoxicity threshold (vide 3) supra) the degree to which formaldehyde promotes its own carcinogenesis may lead to qualitative, as well as quantitative, differences in response within different regions of the dose-response curve.

An argument can be made that any initiating effects of formaldehyde would, nonetheless, produce a population of latent malignant cells. These cells could then produce malignancies in response to other promoters (endogenous or exogenous) as the animals grew older. In such a case the difference in response to formaldehyde exposure at different exposure levels would be only quantitative and not qualitative. This argument is a classical one (See Weisburger and Williams, 1981, supra) and has some merit as a general argument. It needs to be discussed, however, in the context of formaldehyde as it affects the nasal mucosa.

Clearly, in the absence of detoxifying mechanisms, the endogenous levels of formaldehyde should be potentially capable of initiating some cells. The observed absence of nasal carcinomas in rodents as spontaneous tumors (for example, Dr. A. Upton communicates by letter of August 17, 1981, that in 14 years with 1,920 rats he has not observed a single grossly visible nasal carcinoma) indicates one of

four things: (a) no cells are in fact initiated by endogenous levels of formaldehyde or repair processes at low exposure are faster than processes leading to cell transformation; (b) there are not endogenous promoters available to allow expression of the transformed cells; (c) any cells initiated are lost before their malignant potential can be expressed or (d) the tumor incidence is so low as to be undetectable.

The first situation would de facto, define a practical threshold for genotoxicity. Formaldehyde is an endogenous metabolite and it is possible that mammalian cells may deal effectively with low levels of it.

The second situation could suggest that promotion by exogenous factors (formaldehyde could be one) was the controlling element in formaldehyde carcinogenesis. This would imply a lack of carcinogenic effects at exposures to exogenous factors which did not result in promotion. The observation, by CIIT, that tumor formation could be secondary to a formaldehyde induced cytotoxicity, hyperplasia, and metaplasia does suggest that the promoting effects of formaldehyde may be quite important. At low exposure levels the hyperplastic, metaphastic, and cytotoxic effects observed were reversible in the CIIT study.

The third situation is probably relevant to the question of formaldehyde carcinogenesis. Normally, the epithelia of the nasal mucosa loses matured cells which are then daily replaced by underlying stem cell layers. Thus, cells which might be initiated by formaldehyde could be lost from the epithelia before their malignant potential could be expressed. This possibility has not however, been addressed experimentally.

The fourth consideration may have some bearing but in a variety of studies (CIIT and those of Dr. Upton's colleagues at NYU) over 2,000 rats have been observed as a historical control. If nasal carcinoma occurs spontaneously in rats, its incidence would be very low. (See footnote 4)

The observed lack or low incidence of spontaneous nasal carcinoma in rats--given the endogenous levels of formaldehyde present--is probably explained by a combination of the above

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(4) One rat developing a tumor per 2,000 animals would be an incidence of 5×10^{-4}. This is not the same as the level of risk to rat or, possibly, human but suggests that individual risk from endogenous tissue levels of formaldehyde might be bounded by numbers of similar magnitude.

considerations. The net result is that there would appear to exist some lower bound to the observable carcinogenic effect of formaldehyde resulting from exposure to exogenous sources.

As such, the above considerations regarding endogenous levels of formaldehyde coupled with observations of CIIT of the reversibility of formaldehyde related effects at low exposure levels suggest that low level exposures (<1-2 ppm) probably would not present a significant risk of a carcinogenic outcome. The CIIT radio-isotope work also would suggest that carcinogenic risk from airborn formaldehyde could be restricted to the nasal and oral cavities. According to IARC documents there is nearly an 80% site concordance between humans and animals for those human carcinogens adequately testing in animal systems (L. Tomatis et al, Cancer Res. 38, 877 (1978)).

Considertion of Existing Epidemiology Data - A number of small scale retrospective epidemiology studies on groups occupationally exposed to formaldehyde have found no excess of cancers of any type, in particular nasal or oral, in these groups which can be attributed to formaldehyde exposure when corrected for smoking and drinking. The annual incidence of human nasal cancer is about one in one million (1×10^{-6}). While I recognize the limits of sensitivity inherent in epidemiology, such data are useful. In particular, for chemicals of long standing and well defined use, epidemiology could tell if a critical situation exists. If formaldehyde were a potent human risk, this should show up epidemiologically. There does not appear to be any relationship, based on the existing data base on humans, between exposure and cancer. Real human risk could be considered to be low on such a basis.

Human Exposure to Formaldehyde - Human exposure to formaldehyde is at levels generally much lower than those used in the rat inhalation studies. Typical values are ca. 0.005 - 0.3 ppm in ambient air in urban areas, 0.0004 - 0.005 ppm in rural locations, and 0.1 ppm in urea-formaldehyde (UF) foam insulated dwellings. It has not been possible to demonstrate a statistically significant difference in exposure levels in UF foam homes as opposed to non-UF homes. Occupational exposures can be higher but are generally less than 2 ppm formaldehyde. These occupational exposures are, also, for short periods and of an intermittent nature. Table II presents a distribution analysis of exposure levels.

TABLE II: FREQUENCY DISTRIBUTION OF EXPOSURE ESTIMATES IN FORMALDEHYDE PRL-1 TECHNICAL DOCUMENT

These data are extracted from the integrated exposure assessment in the PRL-1. Only estimates given for populations of a known size are considered. High and low refer to the upper and lower bounds of estimated exposure ranges.

INTERVAL (ppm)	Number of estimated exposed individuals			
	Low	Percentage of Total Individuals Exposed	High	Percentage of Total Individuals Exposed
0 - 0.1[b]	2.24×10^8	99.4[a]	2.20×10^8	97.6[a]
0 1 - 0.5	7.09×10^4	0.03	4.50×10^4	0.02
0.5 - 1.0	3.00×10^4	0.01	-	
1.0 - 2.0	3.04×10^4	0.01	5.89×10^4	0.03
2.0 - 5.0	1.24×10^6[c]	0.55	3.86×10^6[d]	1.71
5.0 -	-	-	1.26×10^6[e]	0.56

a/ % of total individuals exposed

b/ includes U.S. population via ambient air

c/ 97% are college students who on an average are exposed to an estimated 8.3 ppm for very short periods and over a limited time. Humans cannot tolerate formaldehyde exposures above 5 ppm and so this group is probably exposed to far less than the PRL-1 average estimate.

d/ 57% are mobile home residents at an average 0.4 ppm; 40% are U.F. home residents at an average of 0.72 ppm

e/ 95% are the same college students as in footnote c.

Humans do not adapt to levels of airborne formaldehyde over 5 ppm and levels from 2 - 5 ppm are generally very unpleasant. The "high" side of the PRL-1 exposure ranges should, then, be viewed critically as this suggests a very sizeable group is exposed - on a regular basis - to levels of formaldehyde above 2 ppm. It must be noted that for the group footnoted as (d) in Table II, the "high" value derives from short transients in complaint homes and is non-representative. The appropriate averages are indicated in the footnote. The exposure group footnoted as (e) in Table II, similarly is constituted by using a single excursion, transient as an upper bound on the range of exposure. The footnote (c) explains that PRL-1 assigned these college biology students an average exposure of 8.3 ppm several hours a week. Clearly, this number is not to be relied on since humans cannot breathe in such an environment. The column listed under "low" is to be taken as more representative (with the possible exception of the college biology students). Table II suggests, then, that nearly all prolonged human exposures are at levels well below 2 ppm.

Given that quantitative and possibly qualitative results of exposure to formaldehyde appear to depend highly on exposure level, species, and route; that rats seem to be particularly sensitive to formaldehyde; and that long human experience does not seem to indicate any pressing concerns; I must concur with OTS' staff recommendations in this matter - that formaldehyde ought not be considered subject to TSCA section 4(f) at this time.

Deficiencies in the Original OTS PRL-1 Document:

The original review of formaldehyde (PRL-1) was deficient in a number of areas -

(1) Exposure Estimates: This was the major deficiency in the original document. In many situations the exposures given were not obtained by analytical methods similar to that used to monitor formaldehyde levels in the CIIT study. No attempt was made to address the comparability of methods so it is not clear that 1 ppm by any given method equates to 1 ppm exposure under the CIIT protocol. This has the effect of making any subsequent risk analysis (which must be exposure based) an "apples and oranges" comparison. Table III points out the various methodologies cited in studies covered by the PRL-1 document.

TABLE III: Number of Exposure Estimates by Type of Analytical or Collection Method in Formaldehyde PRL-1

METHOD	NUMBER OF ESTIMATES	BASED ON METHOD[a]
		as % of all studies
Acetylacetone	1	1.1%
Bisulfite impingers	18	20.7%
Chromotropic acid	17	19.5%
Chemiluminescence	3	3.4%
Colorimetry	7	8.0%
Charcoal tubes	9	10.3%
Solid sorbents	1	1.1%
Draeger Tubes	3	3.4%
FT Spectroscopy	2	2.3%
Gas Chromatography	1	1.1%
Ion Chromatography	7	8.0%
MBTH Method	1	1.1%
Spectrophotometry	3	3.4%
Not Known	14	16.1%

[a]Number of studies in data base which cite a particular method. Some studies cite more that one method.

The PRL-1 review also used the highest values of formaldehyde found in any given monitoring study as its exposure levels for risk analysis. This is not well advised since these high levels are in most cases transients or single excursion values (i.e.: not continuous) and do not, therefore, represent the risk picture adequately. The tendency of the PRL-1 to use exposure levels greater than 2 ppm when calculating exposure to some populations is flawed as well since humans do not well tolerate exposures to formaldehyde which are higher than around 2 ppm. Even though some adaptation can occur, this is unknown above 5 ppm yet PRL-1 uses exposure levels above 5 ppm as prolonged exposures.

The poor quality of the exposure estimates is repeatedly acknowledged in the PRL-1 and forms the basis for the recommendations contained in the earlier draft Federal Register notice and action memorandum (see below). As such, any risk estimates given in the PRL-1 must be viewed very skeptically. It is not clear that such estimates would be a reasonable basis to do other than conclude that one needed better exposure data. This, in effect, is what OTS staff originally concluded and is in the earlier Federal Register notice draft of which NRDC has a copy.

(2) Evidence for Carcinogenecity: The PRL-1 concludes that formaldehyde is an animal carcinogen. It downplays a number of negative bioassays which suggest that its effects may depend highly on species, route and site. No attempt was made, also, to address the question of mechanism of action or other physiological/biochemical questions relevant to the extrapolation from rat to human even though such information was available from CIIT.

The discussion of human epidemiology emphasized studies which showed marginal differences in total cancer rates (i.e., the treatment of one study in which one cohort had a slight increase in total cancer tate relative to historical controls but a second cohort showed no such effect. Much was made of the "positive" cohort but the negative cohort was downplayed). No trend was seen toward increases in any specific cancer (as is common for human chemical carcinogens) in any study. The human data do not show signs (such as correlation to a specific tumor) usually seen for a human carcinogen and do not, as is discussed above, generally suggest any specific effect of formaldehyde.

Risk Assessment:

The PRL-1 document contained a risk assessment performed by use of the Crump multistage model and based on the high exposure estimates presented in the PRL-1 document. OTS staff has also calculated a risk analysis based on median (more representative) exposure values. Relative risks are calculated and expressed as 95% upper confidence limits on lifetime risks.

Table IV presents a population distribution of relative individual risks as calculated by OTS staff in PRL-1 using representative (median or average) exposure estimates. Risk is divided into order of magnitude ranges and the size of the affected population falling into each range is given. As can be seen nearly all individual risks fall into the range $1 \times 10^{-6} - 1 \times 10^{-4}$. This places them into a range in which priority action is often not considered. A similar situation exists for populations of unspecified size (Table V). Again, if the human risk were real, the magnitudes of individual risks do not seem to compel a "fast track" approach. This seems to have been recognized in the draft FR notice prepared in 1981 by OTS under Dr. Muir. That notice proposed to engage in a two year effort to collect exposure data so as to refine the risk calculations. This stemmed from the poor quality of the exposure analysis in PRL-1 and the low relative magnitude of the estimated individual risks.

The risk calculation used by OTS included the 5.6 ppm exposure level as a non-zero incidence data point. CIIT has since determined this point to be statistically no different than the 0 ppm and 2.1 ppm exposure results (see Appendix A). If this 5.6 ppm exposure were treated as a zero response point, the risk estimates of Tables IV and V would shift, in distribution, to yet lower values.

The risk estimates in PRL-1, also, do not take into account that tumor formation in rats appears to require a long term, high level exposure and that the human exposures are likely to be relatively short. Workers might see 1 ppm or less intermittently over a 40 year work career assuming no change in occupation (see footnote 5). College students in biology

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(5) The OSHA standard for formaldehyde is 3 ppm but OSHA documents indicate that workplace exposures are generally less than 1.5 ppm. OPTS staff agree that this is an appropriate and representative number as a general upper bound on workplace exposures.

TABLE IV: DISTRIBUTION OF RELATIVE INDIVIDUAL LIFETIME RISKS AS DERIVED FROM PRL-1 FOR FORMALDEHYDE

Range of Risk	Population Size[a]	% of Total	
		A	B
10^{-6} - 10^{-4} (0.003)[b]	2.14×10^{8}	99.9	95.0
10^{-4} - 10^{-3} (0.15)	1.52×10^{5}	0.071	4.1
10^{-3} - 10^{-2} (1.5)	3.13×10^{4}	0.015	0.9
10^{-2} (3)	0	-	-

A: Total of all identified populations

B: Excluding ambient air and water exposures

[a]This table applies only to exposed populations for which a size was estimated in PRL-1

[b]NCI data indicate that individuals of the U.S. population have an average individual lifetime risk of contracting cancer of 3.3×10^{-1}, the number in parenthesis is the % increment above this average represented by a risk in the center of each indicated range save for the last range in which case the % increment is that due to the boundary risk.

TABLE V: DISTRIBUTION OF GROUPS WITH UNSPECIFIED POPULATION SIZE BY RELATIVE RISK INTERVALS

Both maximum likelihood and 95% upper confidence estimates of relative individual lifetime risk are shown. For comparison, according to recent National Cancer Institute figures the absolute risk of contracting cancer over a lifetime is approximately 1/3 or 3.3×10^{-1}. For each risk interval the percentage increase in lifetime risk (assuming the risk estimates are absolutes which they are not) is presented.

Interval		Number of size	Undetermined groups
range	% incremental[a]	MLE[b] Maximum likelihood estimate	ULOC[c] Upper Limit of Confidence
$<10^{-5}$	0.003%	6	0
$10^{-5} - 10^{-4}$	0.03%	3	7
$10^{-4} - 10^{-3}$	0.3%	2	3
$10^{-3} - 10^{-2}$	3%	0	1[d]

a/ % increment above NCI determined lifetime risk of 3.3×10^{-1}

b/ Maximum likelihood estimate

c/ Upper limit of 95% confidence

d/ Represents one group with a 20 fold range in estimated exposures.

labs are, similarly, a large group (1.2 million individuals) which the PRL-1 assumes are exposed over 70 years. In fact, exposure of nearly all of these students would be generally on the order of one year or less.

Another factor not considered in the PRL-1 risk estimates is that the animal evidence would suggest that inhalation of formaldehyde by humans should produce tumors (if any are seen) primarily of the oral, pharyngeal and nasal mucosa (see footnote 3). These are well defined sites for which the limited epidemiological evidence does not suggest an association with formaldehyde exposure under what are poorly documented but probably representative conditions.

In summary, the PRL-1 does serve to identify some possible areas of concern. From a technical standpoint it would appear to be premature to "fast-track" any regulatory actions since we have estimates only on the upper bound of any risks and these do not, when reasonable assumptions are made, appear to be significant. The draft FR notice (discussed below) which was prepared by OTS on the basis of PRL-1 review acknowledged as much by specifying no regulatory actions per se. The proposed response was, rather, to conduct monitoring surveys of the actual exposure conditions so as to better quantitate the risk. This de facto recognizes that the PRL-1 numbers were highly unreliable and that a proper risk assessment had yet to be done. PRL-1 does not seem to sustain a reasonable conclusion that formaldehyde presents a significant risk of cancer to humans.

Deficiencies in the draft Federal Register notice on formaldehyde:

In 1981 OTS drafted a proposed Federal Register notice on formaldehyde for the signature of the Administrator.

This notice presented a logical sequence and I have analyzed the rationale employed as follows:

(A) Formaldehyde is an animal carcinogen;

therefore,

(B) it is a potential human carcinogen.

(C) Formaldehyde is a high volume chemical;

therefore,

(D) it presents wide spread exposure potential.

(E) Some individual exposures are estimated to be high;

therefore,

(F) some exposures are serious.

Given (B), (D) and (F), then

(G) Formaldehyde is a potential human carcinogen that presents serious or widespread exposures;

therefore,

(H) formaldehyde meets the section 4(f) criteria for "significant" risk of "serious" or "widespread" harm.

There are a number of flaws in this line of reasoning. Some are explicitly acknowledged in the draft FR notice but others are more subtle and need to be addressed first:

(1) The meaning of the term "significant" in the draft FR notice is not consistent with the common technical meaning as discussed above. No case is made for other than formaldehyde being a potential or possible human carcinogen. The degree to which this may or may not be an actuality (i.e., the significance of this risk in terms of probability of existence and magnitude if it exists--as discussed under Technical Issues above) is not addressed. Therefore the draft FR notice uses the words "significant" and "potential" synonymously.

(2) The assumption that a high production volume equates with a high or "widespread" exposure potential is very weak. In general, the degree of correlation between production volume and exposure will depend on uses and handling methods. A blanket assumption, as used in the FR draft notice, is not justifiable in the absence of supporting evidence.

(3) The conclusion that some individual exposures are "serious" is premised on faulty assumptions as to exposure levels as previously discussed.

The plain language of the statute calls for initiation of regulatory action under sections 5, 6 or 7 as the response to be made under section 4(f). The proposed gathering of exposure data--the response given by the FR draft--appears to be an acknowledgement that the significance of any risk from formaldehyde has not been reasonably evaluated since, as a result of gathering this exposure data, it is further proposed to evaluate risk to see if further action is appropriate. The premises and conclusions in the FR draft appear to be faulty.

DEHP:

No detailed analysis is presented of the DEHP situation since work culminating in the PRL-1 and draft Federal Register documents was based on incorrect exposure assumptions. The policy analysis given in the section on formaldehyde applies to the DEHP case.

For purposes of discussion and comparison, the risk estimates in the PRL-1 document are given and then discussed briefly:

Table: PRL-1 Risk Estimates

Group	70 yr Individaul Risks	Potential Cases[a] Over 70 years
hemodialysis patients (45,000)	1×10^{-3}	45
hemophiliacs (19,000)	1×10^{-4}	1.9
U.S. population via food (250 million)	7.5×10^{-7}	188
U.S. population via drinking water (250 million)	6×10^{-7}	150
[b]Occupational (as in PRL-1 originally)		
Manufacturing (335)	1×10^{-4}	0.03
Processing (40,000)	1×10^{-4}	4
[b]Occupational (as revised by OTS)		
Manufacturing (335)	1×10^{-5}	0.004
Processing (40,000)	1×10^{-6}	0.04

a Assumes 95% upper confidence limit is an absolute risk, it is in fact relative and an upper bound on any relative risk present.

b Revised on the basis of exposure data presented at the 1980 pthalates conference.

It must be pointed out that the first two groups in the Table are not affected by TSCA since their exposure is a result of contact with medical devices under the purview of FDA. These are also groups

which are at high risk from their diseases and the benefits of these medical devices should probably far outweigh the risks indicated. In any case, they cannot be factored into any analysis of TSCA applicability.

Estimates for the dietary risks to the U.S. population as a whole fall below the range in which regulatory agencies do not take any actions. The exposures were estimated as described in PRL-1 and are of good quality, in my opinion.

The drinking water estimate is the average number contained in PRL-1. I believe it to be representative and, again, the risks are below the range in which we would normally not act.

The original Federal Register document was driven largely by the occupational risks given in the table. The risks begin to push up into the range in which we would normally consider some action (regulatory or non-regulatory) but are, nonetheless, lower than what might push a priority designation. As a result of the 1980 phthalates conference, OTS staff realized that the exposure estimates which had been used to generate these risks were completely incorrect. In essence they postulated a DEHP concentration (as vapor in air) higher than the vapor pressure of DEHP could generate.

The exposures and associated relative risks were recalculated and are given in the PRL-1 Risk Estimates Table as revised occupational risks. With the revision of the occupational exposure numbers reason to take any action with respect to DEHP disappeared.

There has not, since the detection of the errors in occupational exposures, been any reasonable basis upon which DEHP could be considered to pose significant risk to humans - given current use patterns - and I concur with OTS staff that DEHP cannot be recommended to you as a candidate for section 4(f) designation.

As a final comment on DEHP, there are enough anomalies in the result of the NCI bioassay that I remain unpersuaded that DEHP should be considered a human carcinogen.

Appendix A

DATA RELEASED TO

THE INTERNATIONAL AGENCY FOR RESEARCH ON CANCER (IARC)

WORKING GROUP

OCTOBER 19, 1981

Chemical Industry Institute of Toxicology (CIIT)
P. O. Box 12137
Research Triangle Park, NC 27709

FORMALDEHYDE

3.1 Carcinogenicity studies in animals

(b) Inhalation and/or intratracheal administration

Mouse

Groups of 120 male and 120 female B6C3F1 mice, 6 weeks of age, were exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.46, 6.89, 17.59 ng/m^3) formaldehyde (> 97.5% pure) vapor by whole-body exposure for six hours per day on 5 days per week, for up to 24 months. A 90 day sub-chronic study utilized to set the exposure levels demonstrated necrosis of the nasal mucosa and death after 2 weeks exposure to 40 ppm. The number of mice involved in scheduled sacrifices and unscheduled deaths is shown in Table 1. All tissues from control and high exposure mice and multiple sections of nasal cavity and all gross lesions from all low and mid-exposure mice, as well as all tissues from unscheduled deaths in these groups were evaluated histopathologically.

Concentration related effects of formaldehyde exposure on mouse survival were not apparent, however, substantial mortality did occur in all groups of male mice. This was primarily attributed to fighting and ascending urinary tract infections. Exposure of mice to 14.3 ppm formaldehyde vapor resulted in diminished body weight. Using life-table analysis, a number of lesions in the nasal cavity were significantly increased ($p < 0.0167$). These lesions included epithelial dysplasia at 5.6 and 14.3 ppm in males and females; squamous metaplasia at 5.6 and 14.3 ppm in males and 14.3 ppm in females; purulent or seropurulent rhinitis at 14.3 ppm in males and females; and olfactory epithelial atrophy in 14.3 ppm female mice. Squamous cell carcinomas occurred in the nasal cavities of 2 male mice, but no females. Neither life-table analysis nor the Fischer exact test revealed statistical significance (Kerns et al., 1982a,b).

Table 1. Number of formaldehyde-exposed mice involved in scheduled sacrifices and unscheduled deaths

Exposure (ppm)	Sex	Scheduled Sacrifice					Unscheduled Deaths		Total
		6 mo	12 mo	18 mo	24 mo	27 mo	0-24 mo	24-27 mo	
0	Male	10	10	0	21	0	78	0	120
0	Female	10	10	20	31	16	30	4	121
2.0	Male	10	10	1	22	0	77	0	120
2.0	Female	10	10	20	26	12	34	8	120
5.6	Male	10	10	0	19	0	81	0	120
5.6	Female	10	10	20	41	11	19	9	120
14.3	Male	10	10	0	17	0	82	0	119
14.3	Female	10	10	19	28	9	34	11	121

Rats

Groups of 120 male and 120 female Fischer 344 rats, 7 weeks of age were exposed to 0, 2.0, 5.6 or 14.3 ppm (0, 2.46, 6.89 or 17.59 ng/m^3) formaldehyde (> 97.5% purity) vapor by whole-body exposure for six hours per day on 5 days per week, for up to 24 months. A 90 day sub-chronic study utilized to set the exposure levels demonstrated weight loss and mucosal erosions of the nasal turbinate in rats exposed to 12.7 ppm and mortality and ulceration of the nasal turbinates and trachea after 2 weeks of exposure to 40 ppm. The number of rats involved in scheduled sacrifices and unscheduled deaths is shown in Table 2. All tissues from control and high exposure rats and multiple sections of nasal cavity and all gross lesions from all low and mid-exposure rats, as well as all tissues from unscheduled deaths in these groups, were evaluated histopathologically.

Rat survival was adversely affected by exposure to 14.3 ppm. A summary of neoplastic lesions in the nasal cavity is shown in Table 3. Life-table analysis of these data revealed significant increases ($p < 0.0167$) in squamous cell carcinomas in both male and female rats exposed to 14.3 ppm formaldehyde vapor. Significant increases in other neoplasms were not detected in formaldehyde exposed rats. A variety of other lesions were significantly increased in formaldehyde exposed rats. These included epithelial dysplasia at 2, 5.6 and 14.3 ppm in males and females; squamous metaplasia at 2, 5.6, and 14.3 ppm in males and females; goblet cell hyperplasia at 2, 5.6, and 14.3 ppm in males and at 2 ppm and 14.3 ppm in females; hyperkeratosis at 14.3 ppm in males and females; purulent or seropurulent rhinitis at 2, 5.6, and 14.3 ppm in males and at 5.6 ppm and 14.3 ppm in females; squamous atypia at 14.3 ppm in males and females; olfactory epithelial atrophy at 14.3 ppm in males and females; respiratory epithelial hyperplasia at 14.3 ppm in males; goblet cell metaplasia of the olfactory epithelium at 14.3 ppm in males and females; and squamous epithelial

hyperplasia at 14.3 ppm in males. The incidence of tracheal epithelial dysplasia and metaplasia was different from control animals at 14.3 ppm in both males and females. The incidence of squamous metaplasia in the nasal cavity in rats from the 2.0 and 5.6 ppm exposure groups regressed during the three month postexposure period (Swenberg et al., 1980; Kerns et al., 1982a,b).

Table 2. Number of formaldehyde-exposed rats involved in scheduled sacrifices and unscheduled deaths

Exposure	Sex	Scheduled Sacrifice						Unscheduled Deaths		Total
(ppm)		6 mo	12 mo	18 mo	24 mo	27 mo	30 mo	0-24 mo	24-30 mo	
0	Male	10	10	20	54	10	6	6	4	120
0	Female	10	10	20	47	9	4	13	7	120
2.0	Male	10	10	20	50	10	4	10	6	120
2.0	Female	10	10	20	44	10	1	16	9	120
5.6	Male	10	10	20	41	10	3	19	7	120
5.6	Female	10	10	20	41	9	5	19	6	120
14.3	Male	10	10	20	13	5	0	57	4	119
14.3	Female	10	10	19	14	0	0	57	0	120

Table 3. Summary of neoplastic lesions in the nasal cavity of Fischer-344 rats exposed to formaldehyde vapor.

Exposure group (ppm)	0		2.0		5.6		14.3	
Sex	M	F	M	F	M	F	M	F
No. of nasal cavities examined	118	114	118	118	119	116	117	115
Squamous cell carcinoma	0	0	0	0	1	1	51[a]	52[a]
Nasal carcinoma	0	0	0	0	0	0	1[b]	1
Undifferentiated carcinoma or sarcoma	0	0	0	0	0	0	2[b]	0
Carcinosarcoma	0	0	0	0	0	0	1	0
Osteochondroma	1	0	0	0	0	0	0	0
Polyploid adenoma	1	0	4	4	6	0	4	1

[a]Significantly increased over 0, 2.0, and 5.6 ppm (adjusted Cox-Tarone $p < 0.0167$).

[b]One animal also had a squamous cell carcinoma

3.2 Other relevant biological data

(a) Experimental systems

Toxic effects

Acute cell degeneration, necrosis and inflammation, were evident in the nasal cavities of rats exposed to 15 ppm formaldehyde vapor for 1 to 9 days (6 hrs/day) (Swenberg et al., 1982). Initial lesions were most severe on the tips of the maxillo and nasoturbinates. Acute degeneration and sloughing of the respiratory epithelium, with edema and congestion were evident at the end of 1 day's exposure. This was followed by ulceration, necrosis and an influx of inflammatory exudate at days 3-9. Early squamous metaplasia was detected over the naso- and maxilloturbinates, median septum and lateral wall after as little as 5 days of formaldehyde exposure. Examination of turbinates from rats exposed 5 days and allowed to recover for 48 hours demonstrated considerable regeneration. Areas which were frequently ulcerated, such as the lateral wall, had single thin strap cells covering areas normally occupied by 5 or more cuboidal epithelial cells. In contrast to these changes in the respiratory epithelium, mild serous rhinitis was the principal lesion in regions of olfactory epithelium. Mild degenerative and inflammatory changes were also evident in the nasopharynx.

The mouse was similar, but less severe than the rat in its acute response to formaldehyde toxicity. Five days exposure to 15 ppm formaldehyde vapor caused degeneration, focal necrosis and inflammation to the naso- and maxilloturbinates and to the lateral wall, but minimum toxicity to areas lined by squamous and olfactory epithelium. By comparing these acute data with results from the 6 month interim sacrifice (Kerns et al., 1982a,b), it is clearly evident that adaptive changes have occurred. The extent and severity of formaldehyde-induced toxicity diminishes with time. This may be due to changes in respiratory

physiology, as well as alterations at the cellular level, ie. squamous metaplasia, epithelial hyperplasia and increased detoxification pathways.

Effects of formaldehyde exposure on cell turnover

A prominent response to cell loss associated with toxicity is compensatory cell replication. Surviving cells undergo division in order to replace dead cells. Exposure of rats to formaldehyde vapor for 3 days (6 hrs/day) resulted in increased cell replication in rats at 6 and 15 ppm and mice at 15 ppm. No increase was detected in rats exposed to 0.5 or 2 ppm or mice exposed to 0.5, 2 or 6 ppm (Swenberg et al., 1982).

Studies on the distribution and metabolism of formaldehyde in the nasal cavity

Biochemical investigations on the absorption and distribution of ^{14}C-formaldehyde have demonstrated that H_2CO is primarily absorbed in the upper respiratory system (Heck et al., 1982). Following a 6-hr exposure, the amount of $^{14}CH_2O$ absorbed appears to be directly proportional to the airborne concentration. This result is consistent with the high water solubility of CH_2O. It is important as well that the amount of $^{14}CH_2O$ absorbed did not appear to vary following pre-exposure. Hence, these findings, which are based on single exposures, may also be relevant to the chronic toxicity of CH_2O.

The extensive distribution of radioactivity to other tissues indicates that absorbed $^{14}CH_2O$ or its metabolites are rapidly removed by the mucosal blood supply. It is, however, unlikely that this radioactivity is primarily due to $^{14}CH_2O$. Rapid metabolism in the blood and tissues would probably reduce the concentration of free CH_2O to extremely low levels.

The disposition and pharmacokinetic studies indicate that inhaled CH_2O is extensively metabolized. It is likely that folic acid plays an important, perhaps a pre-eminent, role in this incorporation. However, the possibility that $^{14}CH_2O$ may form covalent adducts in vivo, or that $^{14}CO_2$ may itself be incorporated via carboxylation reactions cannot be excluded. The metabolism of inhaled $^{14}CH_2O$ appears to be similar to that which occurs following other routes of administration.

In order to localize this absorption within the nasal cavity, naive or pretreated rats and mice were exposed to 15 ppm ^{14}C-formaldehyde for 6 hours and prepared for whole-body autoradiography. Formaldehyde-associated ^{14}C was heavily deposited in the anterior nasal cavity of rats and mice. The amount of radioactivity correlated well with the distribution of lesions in similarly exposed animals. That is, activity was greatest in regions of respiratory epithelium over the maxillo- and nasoturbinates and the lateral wall. An exception was noted for the ventral portion of the nasal cavity lined with squamous epithelium. Radioactivity was heavily deposited in this area, however, minimal toxicity occurred. This is most likely accounted for by the relative insensitivity of squamous epithelium to formaldehyde intoxication and supports the concept that induction of squamous metaplasia is a host defense mechanism to formaldehyde toxicity. A portion of the radioactivity located in the ventral squamous regions may be the result of muco-ciliary flow and gravity, rather than direct exposure to formaldehyde vapor. As such, the radioactivity may represent covalently bound material rather than reactive formaldehyde. The extent of formaldehyde-associated radioactivity deposited in regions of olfactory mucosa of posterior sections of the nasal cavity was much less, with radioactivity primarily confined to the nasopharynx. No differences were apparent in formaldehyde distribution between naive rats and mice. When animals that had been

exposed to 15 ppm of non-radioactive formaldehyde for 9 days prior to exposure to ^{14}C-formaldehyde were compared to the naive rats and mice, the pretreated mice had less radioactivity (Swenberg et al., 1982).

This decrease in radioactivity is associated with a decrease in minute volume in mice exposed to formaldehyde (Barrow et al., 1982). If the minute volumes for rats and mice exposed to 15 ppm formaldehyde are used to calculate the amount of formaldehyde inspired, and this amount is normalized to the surface area of the nasal cavity (Gross et al., 1982), the "dose" of formaldehyde available for absorption is 0.154 and 0.075 ug/min/cm^2 in rats and mice, respectively (Barrow et al., 1982; Swenberg et al., 1982). Thus, the mouse nasal mucosa is exposed to half the amount of formaldehyde than the rat nasal mucosa is. This dose correlates well with tumor data, where the incidence of nasal carcinoma is similar in rats exposed to 5.6 ppm and mice exposed to 14.3 ppm of formaldehyde vapor (Kerns et al., 1982b).

Mutagenicity and other short-term tests

The effects of formaldehyde were evaluated in the C3H/10T½ Cl 8 cell transformation system. Treatment of cells with 0.1 - 2.5 µg/ml of formaldehyde alone did not result in significant rates of transformation. If formaldehyde treatment was followed by continuous treatment with 0.1 µg/ml of the tumor promoter 12-O-tetradecanoyl phorbol-13-acetate (TPA), transformed foci were produced. Methanol and formic acid lacked significant transforming activity under either treatment regimen. The results suggest that formaldehyde is an initiating agent for C3H/10T½ Cl 8 transformation (Ragan and Boreiko, 1981; Boreiko and Ragan, 1982; Boreiko et al., 1981).

Formaldehyde has been shown to cause DNA-protein crosslinks in mouse L1210 cells (Ross et al., 1981; Ross and Shipley, 1980) and V79 cells (Swenberg et al., 1982). The DNA-protein crosslinks were repaired within 24 hours in both cell types.

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

FEB 1 2 82

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: OTS Formaldehyde Workplan

FROM: John A. Todhunter, Ph.D.
Assistant Administrator
for Pesticides and Toxic Substances (TS-788)

TO: The Administrator (A-100)

As a follow-up to the analysis and report memo on formaldehyde I recently prepared at your request, I have attached a copy of the Office of Toxic Substances formaldehyde workplan which I recently approved.

Basically, it is proposed to place into action most of the items contained in the draft Federal Register document which was prepared last spring (1981) when there was some confusion as to whether or not formaldehyde was a TSCA section 4(f) chemical. At that time it was believed in OTS that regulations were inappropriate and unsupportable. OTS was faced with the possibility that formaldehyde might set off section 4(f) and, to be ready in case it did, drafted the referenced Federal Register document. Due to OTS' position at that time vis a vis regulation of formaldehyde, the Federal Register document draft posed no regulatory options but, instead, proposed actions of the sort included in the attached workplan.

Allow me to point out that item I, Evaluation of hazard, is underway and part A thereof is essentially completed with part B nearing completion. Parts II and III would develop over a 24-30 month period. They would be supported by part IV.

As was pointed out in my analysis memo, OTS does not recommend that formaldehyde be given priority status - relative to other OTS concerns - under section 4(f) of TSCA. This only indicates that OTS does not hold the carcinogenic risk to be of pressing concern. There could be other, non section 4(f), health concerns (given formaldehyde's irritant properties) and, also, a small possibility that there could be some, as yet unidentified, small subpopulation whose exposure might raise a question of carcinogenic risk we might have interest in pursuing. For these reasons, even though OTS and I agree that we cannot recommend section 4(f) status for this chemical, OTS and I agree that a workplan would be prudent so as to maintain an Agency presence in this matter.

PLAN FOR THE FORMALDEHYDE INVESTIGATION

OUTLINE

I. Evaluation of hazard

   A. Analysis of available animal data to evaluate its relevance for assessing carcinogenicity in humans

   B. Analysis of existing and planned epidemiologic studies and identify the need for additional studies

II. Evaluation of exposure

   A. Update of the exposure assessment

III. Evaluation of risk

   A. Comparative analysis of various risk models

   B. Time-to-tumor analysis

   C. Calculation of risks based on the updated exposure assessment

IV. Establishment of mechanisms for exchange of information

   A. Establish interagency workgroup

   B. Publish Federal Register notice requesting information

   C. Contact and meet with industry and labor groups

V. Outside peer review of hazard, exposure, and risk evaluations

PLAN FOR THE FORMALDEHYDE INVESTIGATION
DESCRIPTION OF PROJECTS

I. Evaluation Of Hazard (HERD)

A. Analyze available animal data relating to formaldehyde's carcinogenicity and evaluate its relevance for assessing carcinogenicity in humans. HERD will evaluate data from bioassays, mutagenicity studies, and research conducted to clarify the mechanism of action of formaldehyde. HERD will evaluate the strength of the evidence of formaldehyde's carcinogenicity, identify likely mechanisms of action, and assess the validity of extrapolating from formaldehyde's demonstrated carcinogenicity in animals at high doses to its action in humans at concentrations typical of human exposures.

B. Analyze existing and planned epidemiology studies to evaluate their anticipated usefulness in identifying formaldehyde's human carcinogenicity and identify and evaluate the need for additional epidemiology studies. HERD will evaluate studies planned by the National Cancer Institute to determine the role they will play in predicting formaldehyde's human carcinogenic potential. They will identify and evaluate the value of sponsoring additional epidemiology studies.

Product: Report describing findings.
Time for completion: 8 months.

II. Evaluation of Exposure (EED)

A. Update and refine the exposure assessment based on available data and identify categories that should be dropped from further consideration. EED will evaluate existing data on population sizes and exposure levels not included in the PRL-1 for accuracy and statistical representativeness, using predictive fate modeling or professional judgment. EED will estimate release levels and exposure levels for categories for which monitoring data are not available. Based on these analyses, EED will identify categories that result in minimal or insignificant exposure and will make recommendations of categories that need not be considered further. The updated exposure assessment will go as far as possible without conducting new monitoring studies. Decisions on any further exposure work will be made after evaluation of risk. It is anticipated that further work may be limited to incorporating information received from contacts and the interagency workgroup described in IV.

Product: Exposure assessment.
Time for completion: 5 months
Extramural funds: less than $25,000.

III. Evaluation of Risk (HERD)

A. Perform a comparative analysis of a number of risk models using the CIIT data, based on hypothetical exposure scenarios. This analysis will show the range of risks that various extrapolation models predict. It will help OTS evaluate the relevance of different models for predicting the risk resulting from exposure to formaldehyde by considering the best fit to the CIIT data and data on biological mechanisms of action. It also will assist OTS in identifying the exposures that are associated with risks of concern. Models to be used include the linear, one-hit, multistage, multihit, probit, logit, and Weibull.

B. Analyze the final CIIT time-to-appearance data using time-to-tumor extrapolation techniques. This analysis will identify whether these techniques improve the accuracy of the risk prediction described in III.A. and will indicate the utility of and resources involved in routinely conducting time-to-tumor analyses. Techniques to be used include the Hartley-Sielken General Product model and Crumps time-to-tumor model. The analyses can be started only after the final data from the CIIT study are available.

C. Recalculate formaldehyde risks based on the updated exposure assessment and the final CIIT data, using appropriate model(s) selected from the analyses performed in III.A. and III.B.

Product: Findings of the comparison of risk models and time-to-tumor analyses and updated risk assessment.
Time for Completion: 8 months.

IV. Establishment of Mechanisms for Exchange of Information (AD)

A. Establish an interagency workgroup to share information and to serve as a conduit to receive the results of research conducted by agencies, industry, and scientific groups as it becomes available. The workgroup will assure that information related to the hazard, exposure, and release of formaldehyde from products is shared by the agencies to avoid overlapping or duplicative efforts.

B. Publish a notice in the Federal Register requesting information relating to hazard and exposure. The notice will describe EPA's interest in obtaining information and will request comment and contact with interested parties. The Federal Register notice will alert academic and international groups not directly involved with the affected industries of our desire for their input and comments.

C. Identify and contact industry and labor groups. OTS will hold a series of meetings with these groups to obtain information about hazard concerns, current exposure levels, production processes, and other technical information. These contacts will be maintained throughout the course of the investigation to assure their continued input.

V. Outside Peer Review of Hazard, Exposure, and Risk Evaluations

A. Each of the new evaluations developed in sections I, II, and III will undergo internal and external scientific peer review in accordance with Agency guidelines.

SCHEDULE (Starting January 4, 1982)

Elapsed Time: 5 months:

- Updated exposure assessment completed.
- Interagency group established.
- Federal Register Notice published.
- Decision to eliminate certain exposures from further consideration, based on the exposure assessment made.

Elasped Time: 8 months:

- Hazard evaluation completed.
- Risk assessment completed.
- Identification of relevant industry and labor groups, and meetings begun.
- Decisions made, such as the extent of OTS' continuing formaldehyde efforts, based on the conclusions of the hazard evaluation; whether to eliminate additional exposures from further consideration, based on the risk assessment; whether or not to conduct additional hazard or exposure studies.

Elapsed Time: 11 months:

- Report on progress and information from interagency group and public contacts.

Elapsed Time: 14 months:

- Peer reviewed reports on new information available on formaldehyde's hazard, exposure, and risk.
- Disposition meeting to decide the direction of the investigation and further research needs, based on the findings to date.