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TOXICOLOGICAL REVIEW OF FORMALDEHYDE - INHALATION ASSESSMENT

(CAS No. 50-00-0)

In Support of Summary Information on the Integrated Risk Information System (IRIS)

VOLUME I of IV

Introduction, Background, and Toxicokinetics

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U.S. Environmental Protection Agency
Washington, DC

~~The extrapolation to humans in terms of using formaldehyde flux to tissue as the dose metric is shown in Table 5-24, where unit risk in terms of q1*, the statistical upper bound on the coefficient, q1, of the term linear in dose in the multistage model, is also presented. q1* is presented even though this is no longer done, as per current EPA practice (see Section 5.3.6 for discussion).~~

~~These results are to be compared with the preferred benchmark estimates obtained in Table 5-23 by using the results of biologically based models. In summary, the unit risks obtained by various methods, including the results in Schlosser et al. (2003), fall within a rather tight range. In particular, q1* was obtained to within a factor of two of other values even though q1 itself was zero. The general result may be noted here, that even in cases where q1 is zero, the upper bound q1* is linear with dose (Subramaniam et al., 2006; Guess et al., 1977). The large difference between q1 and q1* aptly reflects the large uncertainty in the low-dose response.~~

5.4. CONCLUSIONS FROM THE QUANTITATIVE ASSESSMENT OF CANCER RISK FROM FORMALDEHYDE EXPOSURE BY INHALATION

5.4.1. Inhalation Unit Risk Estimates Based on Human Data

As described in Section 5.2, a (plausible upper bound) lifetime extra cancer unit risk of 1.1×10^{-2} per ppm (8.8×10^{-6} per $\mu g/m^3$) of continuous formaldehyde exposure was estimated for NPC incidence using the log-linear modeling results (for NPC mortality from cumulative exposure) from a high-quality occupational epidemiologic study in a life-table analysis to obtain a POD and then applying linear low-dose extrapolation from the POD. Using similar methods and data from the same study for Hodgkin lymphoma and leukemia mortality from cumulative formaldehyde exposure, (plausible upper bound) lifetime extra cancer risk estimates of 1.7×10^{-2} per ppm (1.4×10^{-5} per $\mu g/m^3$) for Hodgkin lymphoma incidence and 5.7×10^{-2} per ppm (4.6×10^{-5} per $\mu g/m^3$) for leukemia incidence were derived. Sources of uncertainty in these estimates are discussed in sections 5.2.2.4 and 5.2.3.4. For the incidence risk for these three cancer types combined, a total (upper bound) cancer unit risk estimate of 8.1×10^{-2} per ppm (6.6×10^{-5} per $\mu g/m^3$) was obtained (see Section 5.2.4).

~~5.4.2. Inhalation Unit Risk Estimates Based on Rodent Data~~

~~As described in Section 5.3, the unit risk derived for SCC in the upper and lower respiratory tract (combined) based on linear extrapolation from PODs from several plausible models, including purely statistical modeling (nose only, quantal and time-to-tumor modeling) and biologically based modeling (entire respiratory tract), resulted in a narrow range of~~

~~1.2×10^{-2} to 2.2×10^{-2} per ppm. Risk to the lower respiratory tract was numerically insignificant compared to the nasal cancer risk.~~

5.4.3. Summary of Inhalation Unit Risk Estimates

The epidemiologic and rodent inhalation data indicate multiple sites of concern. Unit risk estimates calculated separately from these data are presented in Table 5-26.

As can be seen in the summary table (see Table 5-26), the unit risk estimate based on human data for NPC is in the range of the estimates calculated for respiratory tract cancer from the rodent nasal cancer data. The unit risk estimate for Hodgkin lymphoma is also in the same range, while the unit risk estimate for leukemia and the total cancer unit risk estimate are up to fourfold higher.

As noted in EPA's *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), when high-quality human data are available, they are generally preferred over laboratory animal data for quantitative risk assessment. Thus, the preferred (plausible upper bound) unit risk estimate in this assessment is the value of 8.1×10^{-2} per ppm (6.6×10^{-5} per $\mu g/m^3$) based on human data for NPC, Hodgkin lymphoma, and leukemia.

As documented in Section 4.5, formaldehyde is a mutagenic carcinogen and the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA. Therefore, since there are no adequate chemical-specific data to evaluate the susceptibilities of different life stages by the inhalation route of exposure, increased early-life susceptibility should be assumed, and, if there is early-life exposure, the ADAFs should be applied, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). See Section 5.4.4 below for more details on the application of the ADAFs.

The inhalation unit risk estimates presented above, which are calculated based on a linear extrapolation from the POD (95% lower confidence bound on the EC), are expected to provide upper bounds on the risk of cancer incidence. However, for certain applications, such as benefit-cost analyses, estimates of "central tendency" for the risk below the POD are desired. Extra risk estimates per ppm based on linear extrapolation from the EC (e.g., $0.005/EC_{005}$) for the cancer responses based on the human data are reported in Table 5-27. Note that these extrapolated risk estimates are not central tendency estimates in any statistical sense because once risk is linearly extrapolated below the EC, it is no longer a function of the original (Cox regression) model which generated the ECs and the LECs. These estimates are dependent on the suitability of the EC estimates as well as on the applicability of the linear low-dose extrapolation. The assumption of low-dose linearity is supported by the mutagenicity of formaldehyde (see Section

4.5.3). [If

Table 5-26. Summary of inhalation unit risk estimates

Cancer type[a]	Dose metric	Unit risk estimate (ppm^{-1})
Based on epidemiologic data		
Nasopharyngeal	Cumulative exposure	0.011
Hodgkin lymphoma	Cumulative exposure	0.017
Leukemia	Cumulative exposure	0.057
Total cancer risk[b]	Cumulative exposure	0.081
Based on experimental animal data		
SCC of the respiratory tract	Local dose (flux) of formaldehyde in $pmol/mm^2$-hour	0.011–0.022

[a]The unit risk estimates are all for cancer incidence.
[b]The total cancer unit risk estimate is an estimate of the upper bound on the sum of risk estimates calculated for the 3 individual cancer types (nasopharyngeal cancer, Hodgkin lymphoma, and leukemia); it is not the sum of the individual (upper bound) unit risk estimates (see Section 5.2.4).

these estimates were to be used for benefit-cost analyses or some other purpose, ADAFs should be applied, as appropriate, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b), as discussed above and in Section 5.4.4.]

~~5.4.4. Application of Age-Dependent Adjustment Factors (ADAFs)~~

~~When there is sufficient weight of evidence to conclude that a mutagenic MOA is operative in a chemical's carcinogenicity and there are inadequate chemical-specific data to assess age-specific susceptibility, as is the case for formaldehyde (by inhalation exposure; see Section 5.4.3), EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b) recommends the application of default ADAFs to adjust for potential increased susceptibility from early-life exposure (see U.S. EPA [2005b] for detailed information on the general application of these adjustment factors). In brief, EPA (2005b) establishes ADAFs for three specific age groups: 10 (for <2 years), 3 (for 2 to <16 years), and 1 (for 16 years and above). For risk assessments based on specific exposure assessments, the 10-fold and threefold adjustments to the unit risk estimates are to be~~

exposure level of 1 µg/m^3 from ages 0–70 years

Age group	ADAF	Unit risk (per µg/m^3)	Exposure concentration (µg/m^3)	Duration adjustment	Partial risk
0 to < 2 years	10	6.6×10^{-5}	1	2 years/70 years	1.9×10^{-5}
2 to < 16 years	3	6.6×10^{-5}	1	14 years/70 years	4.0×10^{-5}
≥ 16 years	1	6.6×10^{-5}	1	54 years/70 years	5.1×10^{-5}
				Total risk =	1.1×10^{-4}

(Note that the partial risk for each age group is the product of the values in columns 2–5 [e.g., $10 \times (6.6 \times 10^{-5}) \times 1 \times 2/70 = 1.9 \times 10^{-5}$], and the total risk is the sum of the partial risks.)

the ADAFs is to be combined with age-specific exposure estimates when estimating cancer risks from early-life (<16 years age) exposure. Further example calculations can be found in EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b).

In addition to the uncertainties discussed above for the inhalation unit risk estimate, there are uncertainties in the application of ADAFs to adjust for potential increased early-life susceptibility. The ADAFs are general default factors, and it is uncertain to what extent they reflect increased early-life susceptibility for exposure to formaldehyde, if, in fact, early-life susceptibility is increased as assumed. To some extent, the unit risk estimates for Hodgkin lymphoma and leukemia already reflect some partial increased risk from early-life exposure because the life-table programs include background rates for childhood cancers. However, the impact of this partial increased risk is negligible compared to the effect of the ADAFs on the final risk estimate. For example, eliminating the background rates up to age 16 from the life-table programs decreases the lifetime extra risks at the PODs by about 0.5% for leukemia and about 1.2% for Hodgkin lymphoma. The ADAFs, on the other hand, increased the lifetime unit risk estimate by about 66%.

5.4.5. Conclusions: Cancer Inhalation Unit Risk Estimates

As presented in Section 5.4.3, the preferred (plausible upper bound) cancer unit risk estimate for formaldehyde exposure in this assessment is the total cancer risk estimate of **8.1×10^{-2} per ppm (6.6×10^{-5} per µg/m^3) based on (adult) human data for NPC, Hodgkin lymphoma, and leukemia**.

In addition, as described in Section 5.4.4, because the weight of evidence supports the conclusion that formaldehyde carcinogenicity can be attributed, at least in part, to a mutagenic MOA and there are inadequate chemical-specific data to assess age-specific susceptibility, increased early-life susceptibility should be assumed and, if there is early-life exposure, ADAFs should be applied, in accordance with EPA's *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). Consequently, applying the ADAFs to the preferred unit risk estimate to obtain a **full lifetime unit risk estimate** yields

$$0.081/\text{ppm} \times [(10 \times 2 \text{ years}/70 \text{ years}) + (3 \times 14/70) + (1 \times 54/70)]$$
$$= \mathbf{0.13/ppm = 1.1 \times 10^{-4}/(\mu g/m^3)}$$

Using the above full lifetime unit risk estimate of 0.13 per ppm, the lifetime chronic exposure level of formaldehyde corresponding to an increased cancer risk of 10^{-6} can be estimated as follows: $(10^{-6})/(0.13/\text{ppm}) = 7.7 \times 10^{-6}$ ppm = 0.008 ppb = 0.009 μg/m^3. Similarly, the lifetime chronic exposure level of formaldehyde corresponding to an increased cancer risk of 10^{-4} is 0.8 ppb, or 0.9 μg/m^3. (Note that for less-than-lifetime exposures scenarios [or for exposures that vary with age], the adult-based combined estimate of 0.081 per ppm should be used, but if there is early-life exposure, the ADAFs should be applied in accordance with EPA's *Supplemental Guidance* [see Section 5.4.4]).