



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**

June 2, 2010

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U.S. Environmental Protection Agency
Washington, DC

1 4.5.3). [If

2 **Table 5-26. Summary of inhalation unit risk estimates**

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

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^aThe unit risk estimates are all for cancer incidence.

^bThe 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

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Table 5-27. Extra risk estimates per ppm based on ECs^a

Cancer type	BMR ^b	Outcome	EC (ppm) ^c	BMR/EC _{BMR} (per ppm) ^c
nasopharyngeal cancer	0.0005	mortality	0.15	3.3×10^{-3}
		incidence	0.074	6.8×10^{-3}
Hodgkin lymphoma	0.0005	mortality	0.15	3.3×10^{-3}
		incidence	0.051	9.8×10^{-3}
leukemia	0.005	mortality	0.22	2.3×10^{-2}
		incidence	0.16	3.1×10^{-2}
Total cancer ^d		mortality		2.4×10^{-2} ^d
		incidence		4.7×10^{-2} ^d

^aBased on all person-years. Values based on exposed person-years only would be virtually identical.

^bBMR = benchmark response, i.e., extra cancer risk level used to calculate the ECs and LECs.

^cTo convert ppm to $\mu\text{g}/\text{m}^3$, multiply by 1,230; to convert ppm^{-1} to $(\mu\text{g}/\text{m}^3)^{-1}$, divide by 1,230.

^dThe extra risk estimates per ppm for total cancer are not derived from ECs but rather from the calculations of combined cancer risk at 0.1 ppm presented in Section 5.2.4 (see Table 5-20 for mortality and Table 5-21 for incidence). The sums of the MLEs of risk from Tables 5-20 and 5-21, multiplied by 10 to convert from per 0.1 ppm to per ppm, correspond to the extra risk estimates per ppm calculated from the ECs (in that they are based on MLEs and not bounds) but they are not equivalent to the sum of the EC-based values because those are calculated at different ECs and the MLEs of risk are all calculated at a common exposure level of 0.1 ppm.

combined with age-specific exposure estimates when estimating cancer risks from early-life (<16 years age) exposure. The ADAFs and their age groups may be revised over time. The most current information on the application of ADAFs for cancer risk assessment can be found at www.epa.gov/cancerguidelines.

For inhalation exposures, assuming ppm equivalence across age groups (i.e., equivalent risk from equivalent exposure levels, independent of body size) and using the preferred unit risk estimate of 6.6×10^{-5} per $\mu\text{g}/\text{m}^3$ from Section 5.4.3, the calculation is fairly straightforward. For example, the ADAF-adjusted total cancer unit risk estimate for a constant lifetime exposure level is calculated as shown in Table 5-28.

This 70-year risk estimate of 1.1×10^{-4} for a constant exposure of $1 \mu\text{g}/\text{m}^3$ calculated in Table 5-28 is equivalent to a lifetime unit risk of 1.1×10^{-4} per $\mu\text{g}/\text{m}^3$ (0.13/ppm), adjusted for early-life susceptibility, assuming a 70-year lifetime and constant exposure across age groups. As mentioned above, for risk assessments based on specific exposure assessments, application of

Table 5-28. Total cancer risk from exposure to a constant formaldehyde

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1 exposure level of $1 \mu\text{g}/\text{m}^3$ from ages 0–70 years

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Age group	ADAF	Unit risk (per $\mu\text{g}/\text{m}^3$)	Exposure concentration ($\mu\text{g}/\text{m}^3$)	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}

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

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

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

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25 **5.4.5. Conclusions: Cancer Inhalation Unit Risk Estimates**

26 As presented in Section 5.4.3, the preferred (plausible upper bound) cancer unit risk
27 estimate for formaldehyde exposure in this assessment is the total cancer risk estimate of
28 **8.1×10^{-2} per ppm (6.6×10^{-5} per $\mu\text{g}/\text{m}^3$) based on (adult) human data for NPC, Hodgkin**
29 **lymphoma, and leukemia.**

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

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

13 Using the above full lifetime unit risk estimate of 0.13 per ppm, the lifetime chronic
14 exposure level of formaldehyde corresponding to an increased cancer risk of 10^{-6} can be
15 estimated as follows: $(10^{-6})/(0.13/\text{ppm}) = 7.7 \times 10^{-6} \text{ ppm} = 0.008 \text{ ppb} = 0.009 \mu\text{g}/\text{m}^3$. Similarly,
16 the lifetime chronic exposure level of formaldehyde corresponding to an increased cancer risk of
17 10^{-4} is 0.8 ppb, or $0.9 \mu\text{g}/\text{m}^3$. (Note that for less-than-lifetime exposures scenarios [or for
18 exposures that vary with age], the adult-based combined estimate of 0.081 per ppm should be
19 used, but if there is early-life exposure, the ADAFs should be applied in accordance with EPA's
20 *Supplemental Guidance* [see Section 5.4.4]).