



Risk Assessment Advice for Incorporating Early-Life Sensitivity into Cancer Risk Assessments for Linear Carcinogens

Chronic studies used to determine chemical cancer potency in laboratory animals are typically conducted with juvenile through adult-aged animals. Similarly, human epidemiological data most often are from occupational studies of exposed adults; an exception would be community arsenic studies where early-life exposures are taken into account. When laboratory animals are exposed early in life (e.g., from birth to weaning), the chemical cancer potencies (measured as cancer slope factors; CSFs) are often different from what was found in studies of adult exposures. Typically, but not always, chemical cancer potency is greater when the animals are exposed in early life. For many carcinogens, using CSFs calculated from adult animal studies or adult epidemiological studies underestimates lifetime exposure cancer risk.

The MDH Health Risk Limits Rules (HRL) for Groundwater [Statement of Need and Reasonableness](#) (Minnesota Department of Health, 2008) includes an extended discussion of the available data on early-life-stage testing and lifetime averaging (pages 53–60). As a result of MDH review of the age-dependent variability in carcinogens, the HRL values incorporated potency adjustment factors (AFs) developed by the US Environmental Protection Agency (EPA) for 3 age groups: AF of 10 for ages 0 through < 2; AF of 3 for ages 2 through < 16; and AF of 1 for ages 16 through 70. When assessing total lifetime risk for the HRL values, the adult CSFs (i.e. CSFs determined from exposures of adult people or laboratory animals) were multiplied by these default adjustment factors and combined with exposures for birth through age 70.

For a 70-year lifetime exposure:

$$CSF_{adj-70} = CSF * (2 \text{ yrs} * 10 + 14 \text{ yrs} * 3 + 54 \text{ yrs} * 1) / 70 \text{ yrs}$$

Where:

CSF = adult cancer slope factor in units of $[mg/kg\text{-day}]^{-1}$.

CSF_{adj-70} = age-adjusted cancer slope factor for 70 year lifetime exposure in units of $[mg/kg\text{-day}]^{-1}$.

EPA recommends applying default cancer potency age-adjustments (described above) only to mutagenic carcinogens (USEPA, 2005a; 2005b). These EPA guidelines did not address the following EPA Science Advisory Board (SAB) recommendation:

Certain groups of non-mutagenic carcinogens with known modes of action serve as important examples in support of applying a default factor to non-mutagenic carcinogens when the mode of action is unknown. The Review Panel suggests that the Agency reconsider limiting the application of adjustment factors only to mutagenic agents and instead apply a default approach to both mutagenic and to non-mutagenic chemicals for which mode of action remains unknown or insufficiently characterized.(USEPA, 2004)

The Air Hotspots Program of the California Office of Environmental Health Hazard Assessment (OEHHA) in evaluating the age-adjusted cancer potency (CA OEHHA, 2009), determined that available data suggest the lifetime cancer potency for carcinogens regardless of the mode of action are likely underestimated when early-life susceptibility is not included in models. Separate calculations of the mean variation from adult potency for chemicals with a mutagenic mode of action and all modes of action differ by a small amount.

For 0 through < 2 and 2 through < 16 year-olds the mean cancer potency for mutagens is 10 times and 3 times more potent, respectively, as the adult cancer potency (USEPA, 2005a). For carcinogens regardless of the mode of action, early-life potency is 7 to 8 times and about 3 times as potent, respectively, as adult potency. Differences in calculated means have not been shown to be precise enough to support different default adjustments for carcinogens with specific modes-of-action.

Similar to OEHHA, *the MDH HRL Rule applies the default age-adjusted potency factors to all linear carcinogens regardless of mode of action.* Likewise, where it is adequately demonstrated that the default does not reflect chemical-specific toxicological data, a more specific potency adjustment should be used in lieu of the default adjustment.

If the age-adjusted CSF is applied over different exposure averaging times, the adjustment will be different. For instance, if in deriving an excess lifetime cancer risk for an exposure that is assumed to take place over the first 30 years of life (instead of the 70 years shown above), the age-adjusted cancer slope factor used in the calculation would be:

$$CSF_{adj-30} = CSF * (2 \text{ yrs} * 10 + 14 \text{ yrs} * 3 + 14 \text{ yrs}) / 70 \text{ yrs}$$

When calculating a default 70-year lifetime Cancer Unit Risk:

$$UR_{adj-70} = UR * (2 \text{ yrs} * 10 + 14 \text{ yrs} * 3 + 54 \text{ yrs} * 1) / 70 \text{ yrs}$$

Where:

$$UR = \text{adult unit risk } ((\mu\text{g}/\text{m}^3)^{-1})$$

$$UR_{adj-70} = \text{age-adjusted unit risk for 70 year lifetime exposure } ((\mu\text{g}/\text{m}^3)^{-1})$$

Limitations

MDH risk assessment advice recommends the application of EPA default age adjusted potency to assessments of other routes of exposure in addition to drinking water. The default should not be applied when: 1) data are sufficient to calculate a chemical specific early-life CSF (e.g. cancer HRLs derived for vinyl chloride, dieldrin), 2) the carcinogen dose-response is considered to be non-linear in the appropriate exposure range (e.g. the HRLs derived for chloroform, acetochlor), or 3) the CSF is developed from studies that incorporate exposures during early life (e.g. EPA IRIS draft cancer assessment for arsenic). While MDH understands that agencies may decide to apply the potency adjustment factors to a carcinogen as a default adjustment in order to derive screening values, MDH recommends a complete review of chemical specific cancer data in order to determine if a different numerical adjustment should be made, or none at all. Using the default adjustment to produce a screening value will result in a more conservative (higher calculated risk) screening value than if no adjustment was made.

MDH develops health-based guidance using the best science available at the time of derivation. Health-based guidance derived prior to 2008 did not incorporate potency AFs. Due to limited resources it is not possible to update or derive health-based guidance for all chemicals of interest at this time. Chemicals are prioritized for review based on occurrence in environmental media in Minnesota and toxicity and exposure potential. As noted in the MDH HRL SONAR (2008), children's exposure to chemicals in the environment are not always proportional to adult exposures corrected for body mass. This document only addresses

toxicity adjustments and not exposure. Any risk assessment should also consider adjustment of exposure factors that may be appropriate when evaluating childhood or lifetime risks.

References

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- US Environmental Protection Agency, (2005a). Guidelines for carcinogen risk assessment. Risk Assessment Forum. EPA/630/P-03/001F, March, 2005.
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