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Comments Provided for the Independent Peer Review of Established Reference Doses (RfDs) for Sulfolane

Coupling of Exposure Scenarios to RfD-like Values for Sulfolane

Development of RfD-like values is carried out for a variety of purposes. Frequently, these values are coupled with exposure scenarios to set acceptable or tolerable ("safe") levels to be used in public health protection or environmental regulation and/or remediation, e.g., establishing safe drinking water levels. Data-derived insights regarding relative acute versus chronic toxicity or age-related susceptibility, discussed in the course of the RfD development process, can be particularly useful for informing subsequent decisions regarding the choice of exposure parameters to apply in describing public health protective environmental levels. Data that have bearing on the choice of exposure parameters should be explicitly discussed and noted in the development of the RfD-like value. In my opinion, the available toxicity data base for sulfolane supports neither a concern for irreversible effects of early exposures nor age-specific sensitivity of children at RfD-like levels of exposure. Decision-makers should have the benefit of these toxicology-based insights when choosing to use more or less conservative approaches for coupling exposure scenarios with RfD-like values. Site-specific decisions ultimately determine how the use of toxicity data and exposure parameters will impact remediation goals.

A variety of approaches have been taken to couple exposure scenarios to RfD-like values when setting safe drinking water levels. These range from the use of the chronic RfD-like value (in mg/kg/day) converted to the equivalent of ppb in water, assuming consumption of 2 liters of water per day by a 70 kg human to set a drinking water equivalent level (DWEL), to the application of shorter (acute or subchronic) duration RfD-like values coupled with lower body weights and lower water consumption values to represent exposure scenarios for infants or children for a portion of their lifespan. The DWEL assumes that some fraction of the exposure will be coming through the drinking water route. The recent Health Canada (2014) "Drinking Water Guidance Value for Sulfolane" provides another example of such an approach.

As I have discussed previously[1], the use of an adult body weight and water consumption level has its basis in USEPA Drinking Water Standards and Health Advisories (HA) (USEPA, 2011). In this document a "Lifetime Health Advisory" is defined as "the concentration of a chemical in drinking water that is not expected to cause any adverse non-carcinogenic effects for a lifetime of exposure. The Lifetime HA is based on exposure of a 70-kg adult consuming 2 liters of water per day." One day or ten day health advisories use different assumptions regarding acute responses and a body weight of 10 kg and 1 liter a day consumption to protect infants for short durations of exposure when their body weight and consumption patterns could result in higher relative exposures. However, the assumption is that these short duration, higher exposure concerns are adequately accounted for by use of chronic RfD-like values for longer term (lifetime) exposures. Studies of "community water" consumption support these default values of 2 liters for lifetime exposure and 1 liter for infants' and children's exposure as representing the 80-90th percentile of the population values with mean consumption values being closer to half these values. It is considered fully protective of health to combine a chronic RfD-like value, which by definition is protective against appreciable risk for a

[1] Sulfolane Hazard Characterization – Considerations, William H. Farland, Ph.D., ATS, April 5, 2012

lifetime of exposure for the population, including sensitive subpopulations and life-stages, with exposure values that represent the greatest part of a lifetime exposure. In other words, it is appropriately health protective to assess chronic exposure scenarios for a chemical like sulfolane by using an RfD-like value with an adult body weight and ingestion rate.

An alternative approach has been chosen by the EPA Superfund program. The EPA Superfund program has developed a consensus approach to the calculation of screening levels (SLs) which are developed using EPA risk assessment guidance and can be used for Superfund sites. A discussion of SLs can be found at http://www.epa.gov/reg3hwmd/risk/human/rb-concentration_table/index.htm . The SLs are described as "risk-based concentrations derived from standardized equations combining exposure information assumptions with EPA toxicity data. SLs are considered by the Agency to be protective for humans (including sensitive groups) over a lifetime." In the case of drinking water exposure, SLs include an assumption that the use of a chronic RfD-like value, coupled with an assumption of exposure parameters of 1 liter per day consumption for a 15 kg child, will generate a drinking water SL that is protective for the population with a lifetime of exposure. While the SL takes a more conservative approach, the HA value and the SL differ only by a factor of 2.3 times (70kg/2liters/day divided by 15kg/1liter/day). USEPA is clear to point out that SLs are generic screening values, not *de facto* cleanup standards.

It should also be noted that this 2.3x difference is well within the inherent uncertainty of the RfD-like estimate itself. This difference between the HA and SL approaches can be contrasted with the magnitude of the composite uncertainty factor which renders the estimate of the RfD-like value to be hundreds to thousands of times below observed subtle non-carcinogenic effects in animals, even at human equivalent concentrations (HECs). In the case of the sulfolane data, blood cell effects with unknown toxicologic significance. Additional insights which might inform the choice of drinking water exposure parameters include minimal concern for sulfolane carcinogenicity, based on lack of a proposed mode of action and negative data from the study of a chemical analog. Effects in a reproductive studies are only seen at exposure levels which are higher by an order of magnitude or more. Frank effects after acute exposures have only been observed at even higher levels.

As mentioned previously, exposures at the level of drinking water Lifetime HAs are not expected to cause any adverse non-carcinogenic effects for a lifetime of exposure.   Unlike the case for sulfolane, the SL approach is designed to generate acceptable levels of contaminants for both carcinogenic and non-carcinogenic effects and to account for the possibility of shorter-term, age-specific exposures leading to toxicity, in the absence of test data to address these issues. While some groups, such as ATSDR, have coupled chronic RfD-like values with even lower body weights (10 kg) and low consumption levels (1 liter/day) to set action levels that are purported to be "protective" for infants, given the results of the sulfolane studies and the approach used to derive the RfD-like values, there is no reason to believe that this more conservative approach is warranted to protect public health. Infants and children remain at these average body weights for a short period of time and sulfolane does not accumulate in the body. In addition, unless irreversible or acute responses are predicted, or infants are expected to be unusually susceptible to an observed effect, there is no reason to believe that the less conservative approaches described by the USEPAs Drinking Water Program will not be protective of the entire population, including infants, for a full lifetime of exposure. Neither concern for carcinogenicity nor for short-term, age-specific exposures is applicable given what is known about sulfolane.