**Sulfolane Hazard Characterization – Considerations**

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## Introduction

This set of considerations on the hazard characterization of sulfolane is being prepared at the request of Flint Hills Resources. It is based on an independent assessment of the toxicological data available for sulfolane as well as the various efforts that have been made by others to put these data and observations into a risk assessment context. These considerations rely heavily on the previous efforts but provide a more holistic view in order to assure that decision-makers in Alaska have the information needed to make reasonable, public health-protective judgments regarding potential exposure to sulfolane.

These perspectives represent my collective expertise and experience over more than thirty years as a scientist, toxicologist and risk assessment practitioner. I am currently the Vice President for Research at Colorado State University in Fort Collins, CO. I am also a Professor in the Department of Environmental and Radiological Health Sciences, School of Veterinary Medicine and Biomedical Sciences at that institution. I hold a Ph.D. (1976) from UCLA in Cell Biology and Biochemistry. In 2006, I completed 27 years of Federal service in research and development with the U.S. Environmental Protection Agency, leaving as the Deputy Assistant Administrator for Science. I have served on a number of executive-level committees and advisory boards within the Federal government and in the private sector. I served as Chair of an External Advisory Group for the National Institute of Environmental Health Sciences (NIEHS) on the future of the Superfund Basic Research Program. I currently serve as Chair of a standing committee on emerging science for environmental health decisions of the National Research Council (NRC) of the National Academy of Sciences and a member of an NRC Committee to Develop a Research Strategy for Environmental, Health, and Safety Aspects of Engineered Nanomaterials. In 2002, I was recognized by the Society for Risk Analysis with the "Outstanding Risk Practitioner Award," and in 2005 was appointed as a Fellow of the Society. In 2006, I received a Presidential Rank Award for my service as a federal senior executive. In 2007, I was elected as a Fellow, Academy of Toxicological Sciences. I continue to teach and publish and have been a member of the Editorial Board and reviewer for Risk Analysis, Environmental Health Perspectives and Chemosphere.

## Executive Summary

The database on sulfolane has been evolving over the last three decades. Relatively speaking, compared to other industrial chemicals encountered in the environment, the available data and details of their generation are quite robust. A picture emerges of sulfolane, as a minimally toxic chemical at low levels in a variety of animal test systems. The effects seen a low doses represent subtle changes which are generally considered to be of unclear toxicological significance and may represent reversible, "adaptive" responses rather than precursors to toxicity. The recent

assessments have illustrated the differences in opinion and policy judgments that can arise when subtle effects with questionable toxicological significance lead to identification of points of departure (POD's) for risk assessment purposes. This lack of consensus on which study to use as the "critical study" and the lack of a consistent method of assessment supports the argument that the observations in these studies provide an uncertain basis for health risk assessment and provide "screening-level values" at best. The assessment activities discussed above have produced a provisional health guidance value (ATSDR) and provisional peer-reviewed toxicity values including a provisional RfD (EPA). It is important to remember that these RfD-equivalent values are not boundaries between safety and risk. A variety of uncertainties are present when extrapolating from such effects in animals to human populations and from partial lifetime studies in animals to longer term potential exposures in humans. Many of these uncertainties are inherent in the policy choices available to risk assessors and are compounded when multiple policy choices are chosen in a given assessment like that for Sulfolane. Calculation of a "safe" drinking water level based on such policy choices would result in a level that is thousands of times below the level where the subtlest potential adverse effects were NOT seen in the animal studies and about 11,000 times below the level where these subtle effects of unknown toxicologic significance were seen. This suggests that at these drinking water levels of sulfolane there would likely be no appreciable risk to exposed human populations.

## Toxicity Data Base for Sulfolane

Relatively speaking, compared to many chemicals encountered in the environment, sulfolane has been well studied. The details of these studies and their use in a risk assessment context has been presented previously by the British Columbia Ministry of Water, Land and Air Protection (BCMWLA, 2001); Canadian Council of Ministers of the Environment (CCME, 2006); Alaska Department of Environmental Conservation (ADEC, 2006); ToxStrategies (2009, 2010, 2011); Texas Commission on Environmental Quality (TCEQ, 2011); Agency for Toxic Substances and Disease Registry (ATSDR, 2010, 2011); and US Environmental Protection Agency (USEPA, 2012a). These assessments have considered a historical data base developed over two decades from the mid-1970's to the early 2000's.

Although sulfolane has not been the subject of many studies in the peer-reviewed, published scientific literature, several well conducted studies have been reported and subsequently peer reviewed. The majority of these reports contain sufficient information to judge the details and the quality of the work presented. In the case of the studies by Zhu et al (1987), follow-up evaluations have pointed out the lack of detail in the reporting of these studies and their shortcomings for use in up-to-date risk assessment. Although no lifetime studies are available, the data base is robust with acute, subchronic and developmental/reproductive screening data. One study was a study of six-month duration, which is twice as long as a typical subchronic study. In these studies, multiple species were examined and in several studies, comprehensive pathology evaluation was performed. Acute toxicity data are available from several studies in multiple species by multiple routes. Results suggest an LD 50 value around 2 g/kg/day. To put this dose in perspective, it is equivalent to the "limit test" dose of 2 g/kg/day for acute toxicity that is used nationally and internationally to test chemicals to determine that they have a minimal degree of toxicity.

Aside from frank effects seen in acute studies within an order of magnitude (factor of ten) of the very high doses causing lethality, other manifestations of toxicity are lacking in longer term, lower dose studies. The partial lifetime (subchronic) studies in particular suggest toxicological investigations without appreciable low dose toxicological effects. Carcinogenicity does not appear to be of concern since genotoxicity studies have been mostly negative and a lifetime cancer study in animals of a similar compound (sulfolene) raised no concerns. The focus of attention at low doses in subchronic studies has been on the observation of subtle changes which are generally considered to be of unclear toxicological significance.

An example of the effects that are currently the focus of the assessment process includes the subtle effects seen in the well conducted Huntington Life Sciences study (HLS, 2001). In this study, investigators reported statistically significant decreases in white blood cell (WBC), lymphocyte, monocyte, and large unstained cell counts in female rats given 100 mg/l (10.6 mg/kg/day) or more sulfolane. To put these observations in context, the HLS study investigators concluded that the toxicological significance of the effects on WBC counts was unclear due to the lack of evidence of any chronic inflammatory change or compromised immune function in female rats, even though these decreases were statistically significant relative to the concurrent control animals. In addition, these investigators failed to detect any effects on bone marrow, thymus or spleen that might provide a biological basis for reduced numbers of white blood cells. Despite the fact that the three highest doses produced a statistically significant reduction on WBC counts compared to concurrent controls, the questionable significance of these effects as an indication of toxicity is supported further when the effects are compared to historical control female counts. Using this larger population of control animal values, ToxStrategies (as reported in ToxStrategies' Sulfolane White Paper Update, 2010), demonstrated that the "reduced values" seen in the HLS study were within the range of historical controls. Similarly, the Zhu et al. (1987) study found subtle changes in the liver (fatty deposits) and WBC counts in another test species, the guinea pig. These endpoints, which have been the focus of some risk assessment and health screening values, are considered "non-specific." They are not associated with a particular toxicity or disease and are, in fact, quite common manifestations of adaptive rather than adverse responses. They do not easily project into specific health concerns for exposure to sulfolane.

Differentiation between an adverse effect and an adaptive response is central to toxicology and is a critical determination in the context of toxicity testing approaches. In a recent publication, Keller et al (2012) discuss the importance of this distinction to toxicity testing and risk assessment. The identification of an adverse outcome after xenobiotic exposure has been a mainstay for assessing risk to inform risk management decisions. Adverse effects used for these decisions tend to be apical outcomes such as tumors, permanent changes in the target tissue, or specific transient changes in the target tissue directly associated with the ultimate outcome of concern. This manuscript defines adverse and adaptive responses as follows:

Adverse Effect: A change in morphology, physiology, growth, development, reproduction, or life span of a cell or organism, system, or (sub)population that results in an impairment of functional capacity, an impairment of the capacity to compensate for additional stress, or an increase in susceptibility to other influences.

Adaptive Response: In the context of toxicology, the process whereby a cell or organism responds to a xenobiotic so that the cell or organism will survive in the new environment that contains the xenobiotic without impairment of function.

In the absence of the linkage of observations like those described above with potential human disease outcomes, the distinction between adverse and adaptive becomes blurred and use of these endpoints for other than screening purposes becomes problematic.

**Lack of Scientific Consensus on the Selection and Use of a Particular "Critical Study"**

The most recent assessments from governmental bodies (ATSDR, 2010, 2011; EPA, 2012a) have illustrated the differences in opinion that can arise when subtle effects with questionable toxicological significance lead to identification of points of departure (POD's) for risk assessment purposes. ATSDR's decision as to what study to rely on as the critical study hinged on whether the study had been published in the open literature (the Zhu et al. studies). ATSDR chose to use the Zhu studies to set an "action level" despite the fact that the publications are in an obscure, local Chinese journal, lacked experimental and statistical detail and presented decisions on the level of no observed adverse effect levels (NOAELS) that are unsupported by a statistical analysis of the data. Additional arguments made by ATSDR for use of these studies include an assessment that they report data from a more "sensitive" species, guinea pigs, when compared to observations in rats in the HLS study. EPA in its final PPRTV document does not rely on the Zhu et al. studies despite the fact that several EPA toxicologists participated in the ATSDR document review. EPA states that "This report appears to be an extended abstract of the original study with very little useful information for risk assessment purposes. There is, for example, no clear indication of histopathological examination of any tissues in any test described, save for the spleen and liver in the 6-month study. This lack of results precludes assigning any effect levels at least to the 90-day test reports." In a recent Research Concept document (NTP, 2011), citing similar concerns, NTP opined that evidence that the guinea pig may be more sensitive than rats is "suggestive" at best. In its most recent assessment, ATSDR chose to use a benchmark dose (BMD) approach to determine a POD. Use of a BMD approach is consistent with more modern approaches to risk assessment and moves away from the NOAEL approach that was used in its previous assessment (ATSDR, 2010).

EPA (2012), on the other hand, chose to rely on the HLS (2001) study as its critical study. EPA explains this decision by saying "The methods in the Huntingdon Life Sciences study are well documented, and the study adheres to GLP guidelines. Additionally, the study authors conducted the drinking water study at a lower dose range and examined a wider array of endpoints than the other available studies, and thus, the study was able to detect more sensitive effects of sulfolane." The EPA concluded that confidence in the HLS study was "high." However, despite a variety of available approaches to BMD analysis with precedence in other EPA assessments, including log transformation of the experimental doses, EPA chose to rely on a NOAEL approach to evaluating the HLS data (2001). EPA also chose to use the maximum recommended uncertainty factor for its chronic PPRTV value. EPA's confidence in this value is considered "medium" despite its "high" confidence in the HLS study data.

This lack of consensus on which study to use as the "critical study" and the lack of a consistent method of assessment supports the argument that the observations in these studies provide an uncertain basis for health risk assessment and provide "screening-level values" at best.

## Uncertainty in the RfD-Equivalent Value

EPA, in its Integrated Risk Information System glossary, defines a reference dose (RfD) as an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. It can be derived from a NOAEL, LOAEL, or benchmark dose, with uncertainty factors generally applied to reflect limitations of the data used. The RfD is the approach generally used in EPA's noncancer health assessments. Durations include acute, short-term, subchronic, and chronic and are defined individually in the glossary. Other Agencies, including ATSDR and State Agencies, have adopted similar approaches. As defined, an RfD-equivalent value contains inherent uncertainty of perhaps an order of magnitude and is not a precise value. This uncertainty is considered to extend to approximately a factor of three on either side of the stated value. While operationally, a POD represents a single number, it should be remembered that the POD also contains inherent uncertainty dependent on the dose spacing in the critical study supporting the assessment or on the BMD model used to set the POD.

The assessment activities discussed above have produced a provisional health guidance value (ATSDR) and provisional peer-reviewed toxicity values including provisional chronic and subchronic RfDs (EPA). ATSDR's guidance value has led to their development of an action level for drinking water exposures to sulfolane. In describing its action level, ATSDR says "Simply put, an action level is intended to serve only as a screening tool to help decide whether to evaluate more closely exposures to a substance found at a site (ATSDR 2005). Exceeding the recommended action level supports the need for additional assessment of site conditions." Exceeding the action level should not be construed as representing a true health risk given the uncertainty in the number and the conservative approaches used in its derivation. ATSDR chose to use the 1.5 mg/kg/day Benchmark Dose Low (BMDL) on the dispersion of the spleen's white pulp from the Zhu et al. study. In 2011, ATSDR recommended a total uncertainty factor of 1000 (10 for animal to human extrapolation, 10 for variability in human sensitivity, and 10 for extrapolation of an intermediate dose to a chronic dose), resulting in a sulfolane guidance level of 0.002 mg/kg/day. Despite the fact that the 2011 evaluation was based on the same Zhu et al. results as were used in 2010, the 2011 evaluation incorporated an additional uncertainty factor for intermediate to chronic exposure, as compared with ATSDR's 2010 Health Consultation. The reason given for adding an additional factor of 10 was to account for "the longer duration of exposure apparently occurring at this site." It is unclear why this perspective should be new compared to the 2010 assessment. So, despite the use of a modeling approach which increased the estimate of a POD level likely to be without appreciable risk from 0.25 mg/kg/day to 1.5 mg/kg/day, ATSDR did not significantly change its action level estimates. In essence, this increases the margin of exposure associated with observed subtle effects to well over 1000.

As mentioned above, EPA chose the study by Huntingdon Life Sciences (2001) as the critical study for derivation of the p-RfD (provisional RfD). The critical endpoint is decreased total and differential WBC count in female rats. BMD modeling of total WBC count in female rats was attempted consistent with EPA's BMD technical guidance (USEPA, 2000a). According to EPA (2012), the BMD analysis resulted in significant lack of fit. Because these data were not amenable to BMD modeling according to EPA, a NOAEL/LOAEL approach was employed to identify the point of departure (POD). EPA indicates that the leukocyte data provide a

consistently observed effect, and identifies a NOAEL of 2.9 mg/kg-day in females that can be established as a POD for deriving the oral subchronic and chronic RfDs. The LOAEL for this same effect in females is 10.6 mg/kg-day. EPA applies a total uncertainty factor of 300 and 3,000 for the subchronic and chronic p-RfDs respectively. Each contains uncertainty factors to account for interspecies differences (10X), intraspecies sensitivity (10X), and database sufficiency (3X). The chronic p-RfD contains an extra factor (10X) to account for use of a subchronic study to predict chronic exposure. A composite uncertainty of 3,000 is the maximum recommended composite uncertainty value according to EPA guidance. This is because it is recognized by risk assessment practitioners that individual uncertainty factors are not fully independent and overlap exists among these factors. Use of multiple factors increases the potential for over estimation of relative uncertainty. If the composite uncertainty factor exceeds 3,000, then the database generally does not support development of an RfD (USEPA, 2002), although some early assessments used a composite uncertainty factor of 10,000. A "safe" drinking water level selected using this chronic p-RfD would be 3,000 times below a NOAEL, chosen from a dose in the study that was determined to be without even a subtle effect. Therefore, the drinking water level would be thousands of times below the level where the subtlest potential adverse effects were NOT seen in the animal studies and about 11,000 times below the level where these subtle effects of unknown toxicological significance were seen.

It is important to remember that these RfD-equivalent values are not boundaries between safety and risk. The ATSDR consultation is clear on this point. Human risk is more likely as one approaches the doses producing effects in other animals. If composite uncertainty factors are low, as is the case when human data are available, the probability of effects increases quickly as the Hazard Index exceeds 1. If composite uncertainty factors are large, as in this case, choice of an exposure even an order of magnitude (factor of 10) above the RfD-equivalent screening value likely carries little to no probability of risk of adverse health implications. The use of an animal study to predict effects in humans in the absence of human data is not driven purely by science but is a science policy decision. The selection of specific UFs when developing an RfD-equivalent value also involves science policy. In any risk assessment, a number of decision points occur where risk to humans can only be inferred from the available evidence and science policy decisions are required to bridge this gap. Both scientific judgments and policy choices may be involved in selecting from among several possible inferences when conducting a risk assessment. It is important that these choices are understood and factored into decision-making regarding protection of human health. Simply compounding numerous "conservative" policy choices in the derivation process, in the absence of good scientific reason, can result in decisions which provide no more protection for human health but alarm the public, require unnecessary controls, and have social implications for the community in terms of property values, tax revenues, population growth, etc.

## Coupling of Exposure Scenarios to the USEPA PPRTV or Other RfD-like Values

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 use of an adult body weight and water consumption level has its basis in USEPA Drinking Water Standards and Health Advisories (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 80-90$^{th}$ 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 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 (USEPA, 2012b). 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). This difference is well within the inherent uncertainty of the RfD-like estimate itself and can be contrasted with the magnitude of the composite uncertainty factor which renders the estimate of the RfD-like value to be 1-10,000 times below observed subtle effects in animals. USEPA is clear to point out that SLs are generic screening values, not *de facto* cleanup standards. The SL approach is used to assess acceptable levels of both carcinogenic and non-carcinogenic effects and accounts for the possibility of shorter-term, age-specific exposures leading to toxicity. The available toxicity data base for sulfolane supports neither a concern for irreversible effects of early exposures nor age-specific sensitivity of children. Site-specific decisions determine how the SLs will impact remediation goals.

States have developed their own guidance for deriving screening or clean-up levels. For instance, Alaska's Department of Environmental Conservation has issued an updated draft of its Risk Assessment Procedures Manual (ADEC, 2011). In this manual, the use of RfD-like values in deriving acceptable drinking water concentrations is discussed. The use of the adult weight (70 kg) and water consumption value (2 liters/day) is presented in the example. Similarly, the uncertainty in the estimates is discussed as a critical part of a site-specific human health risk assessment.

While some groups, such as ATSDR, have coupled subchronic and chronic RfD-like values with lower body weights (10 kg) and 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 step is necessary to protect public health. Infants remain at these average body weights for a short period of time and, unless acute responses are predicted or infants are expected to be unusually susceptible to an observed effect, there is no reason to believe that the approaches described above will not be protective of the entire population, including infants, for a full lifetime of exposure. Neither of these reasons is applicable given what is known about sulfolane.

## Use of Defaults in Risk Assessment

Throughout the history of risk assessment, practitioners have embraced the use of default values to limit the number of inference options to be considered, to replace missing or inadequate chemical-specific information, and to allow a risk assessment to continue. In 1983, the authors of the National Research Council's (NRC) report, *Risk Assessment in the Federal Government: Managing the Process* (NRC, 1983) described a default as the inference option "chosen on the basis of risk assessment policy that appears to be the best choice in the absence of data to the contrary." Much debate has surrounded the use of default values in the conduct of risk assessment. In its 1994 report, *Science and Judgment in Risk Assessment*, the NRC discusses the key defaults used by EPA and suggests that they are based on relatively strong scientific foundations, despite the fact that none can be demonstrated to be "correct" for every chemical or situation (NRC, 1994). They represent science policy choices which must be examined in light of available chemical- or site-specific information. This perspective has led to the practice of substance-specific departures from defaults and to discussions around what information, and how much, is needed to reasonably select alternative inferences in individual risk assessments. Over the last decade, EPA's risk assessment guidance has moved toward the examination of all relevant and available data first before making a conscious choice to invoke defaults or standard values (USEPA 2000b, 2004, 2005). This is a different approach from choosing defaults first and then using data to depart from them. This shift in guidance, while well founded, is not without its own controversy. In its 2009 report, *Science and Decisions, Advancing Risk Assessment*, the NRC discussed the importance of continuing to examine the evolving science underlying defaults to ensure their consistency and to define the evidentiary standards for the use of alternative inferences; and suggests the importance of the development of specific criteria for judging alternatives. (NRC, 2009). The heart of this decades' long discussion is that application of default values or standardized assumptions should always be accompanied by the evaluation of their consistency with available data and information. Risk assessments that carefully evaluate available information and rely on scientific judgment, applied to the chemical

constituent and its site-specific exposure characteristics, are typically preferred over risk assessments that make significant use of default positions.

**Assessment of Margins-of-Exposure (M-O-E)**

Risk assessors and decision-makers have often found it informative to compare margins-of-exposure (MOEs) for available PODs as way to put the toxicity data analysis in perspective. MOEs compare the POD divided by anticipated or desired environmental concentrations. With the multiple studies that have been published on sulfolane, a variety of subtle low dose effects have been analyzed as potential PODs. These have included effects on blood cells, male rat kidney, reproductive and developmental effects and spleen and liver effects. Depending on the effect and the approach used for analysis (observed level in a particular study e.g. NOAEL or benchmark dose assessment); different PODs might have been chosen. In the case of blood cell effects from the HLS study, PODs are in the 10's of thousands parts per billion (ppb) drinking water equivalent concentration. For kidney effects in the rats from the MHWJ studies (MHWJ, 1999), which are generally considered to be species-specific effects based on mechanisms seen only in male rats and for the reproductive and developmental effects seen in the same studies and in the Zhu study (Zhu, 1987), PODs are in the 100's of thousands ppb drinking water equivalent concentration. If spleen or liver effects were used as a POD, results from individual studies could range from just over a thousand to a million ppb drinking water equivalent concentration. As illustrated in Figure 1, at concentrations approaching the level of detection (6 ppb) or at levels representing the recent ARCADIS best estimate for a "protective" level in drinking water, MOEs are generally 2-3 orders of magnitude (hundreds to thousands) below where no subtle effect was seen or modeled in several studies. Depending on the study and dose spacing in the protocol, the actual level where these effects were seen could be an order of magnitude greater. This figure illustrates that, using the subtlest of effects seen in the various toxicity studies that have been the focus of risk assessment efforts and a variety of approaches representing best thinking among a variety of risk assessors, the MOE for sulfolane in drinking water is likely to be adequate to protect public health for populations exposed up to the current best estimate of a "protective" level coming out of the ARCADIS assessment.

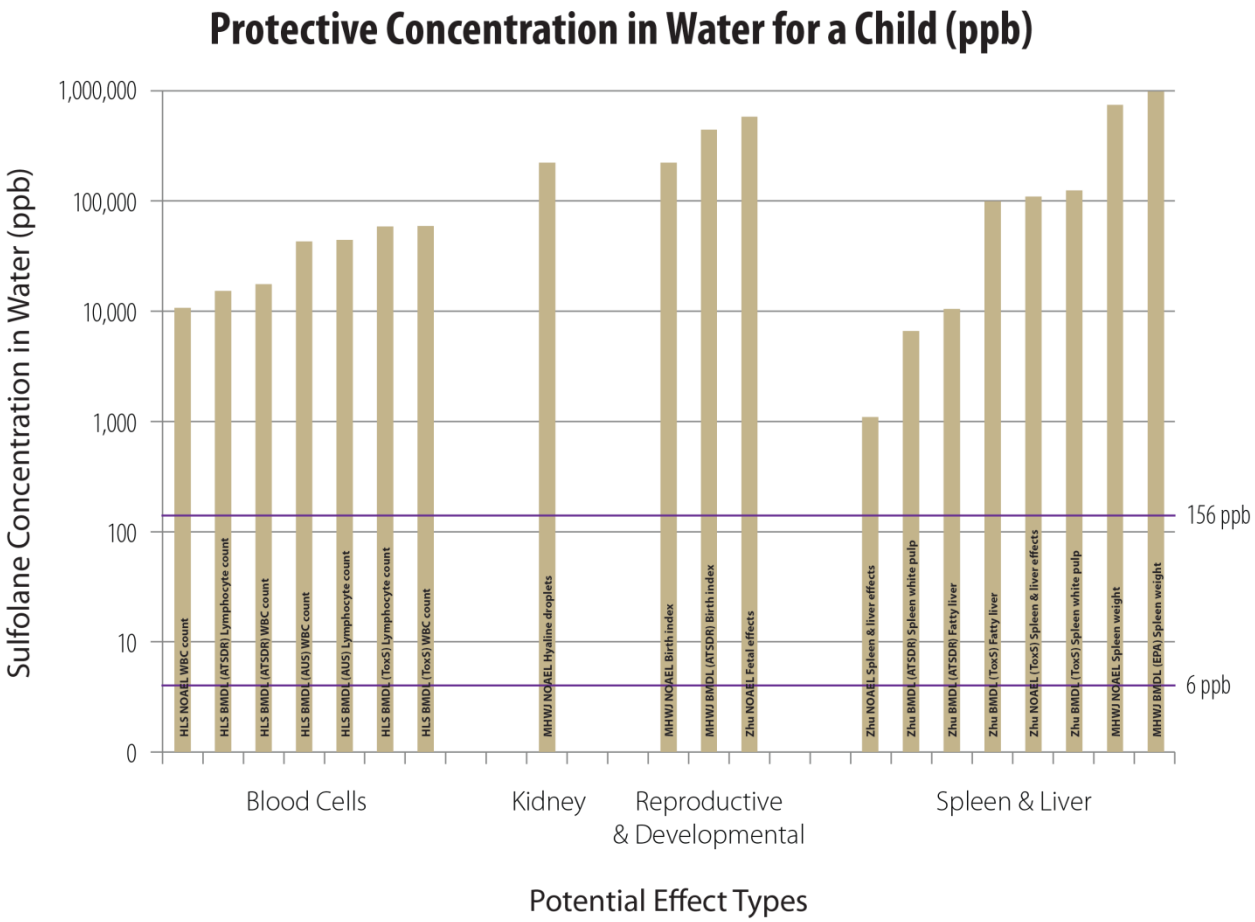


**Figure1. Margins of Exposure (MOEs) based on alternative points of departure and drinking water concentrations (figure courtesy of ARCADIS)**

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