Review of Oral, Chronic Reference Doses for Sulfolane (CASRN 126-33-0)

August 17, 2014

ACRONYMS AND ABBREVATIONS

ADEC	Alaska Department of Environmental Conservation
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower bound 95% confidence interval
BMDS	Benchmark Dose Software
BMR	benchmark response
CCME	Canadian Council of Ministers of the Environment
DHSS	Department of Health and Social Services
FHRA	Flint Hills Resources of Alaska
GLP	Good Laboratory Practices
HED	human equivalent dose
HLS	Huntingdon Life Sciences Ltd.
LUC	large unstained cell
mg/kg	milligrams per kilogram
mg/kg-day	milligrams per kilogram body weight per day
mg/L	milligrams per liter
NOAEL	no observed adverse effects level
NTP	National Toxicology Program
OECD	Organisation for Economic Cooperation and Development
POD	point of departure
ppb	parts per billion
PPRTV	Provisional Peer-Reviewed Toxicity Value
RfD	reference dose
TCEQ	Texas Commission on Environmental Quality
TDI	tolerable daily intake
TERA	Toxicology Excellence for Risk Assessment
UF	uncertainty factor
US EPA	United States Environmental Protection Agency
WBC	white blood cell

ACRONYMS AND ABBREVATIONS

μg/L	micrograms per liter

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1. Introduction

The discovery in late 2009 of sulfolane (2,3,4,5-tetrahydrothiophene-1,1-dioxide, CAS No. 126-33-0) in drinking water wells near the North Pole Refinery, about 15 miles east of Fairbanks, Alaska, has led to an extensive investigation of contaminated groundwater. To date, the plume is nearly 2.5 miles wide and 3 miles long, one of the largest in Alaska. Through 2013, Flint Hills Resources of Alaska (FHRA), the current refinery owner, has provided 305 long-term alternate water supplies at 285 properties in the affected area (Barr Engineering Company 2014). Alaska Department of Environmental Conservation (ADEC) is currently in the process of setting a groundwater cleanup level protective of residential consumption of groundwater containing sulfolane. As part of that review, ADEC has tasked Toxicology Excellence for Risk Assessment (TERA) with conducting an independent, expert peer review of the available chronic, oral reference doses (RfDs) for sulfolane.

This document provides background information on the site and refinery, along with efforts to date. It also briefly describes the multiple sulfolane chronic toxicity values, or RfDs, available. Text in this document has been excerpted from a number of sources, as referenced. For simplicity, in this document and for the peer review, the term RfD will be used to refer to all the various chronic toxicity values developed for sulfolane.

1.1. Site History

In the late 1970s and early 1980s, numerous spills of petroleum product leaked from above-ground bolted storage tanks and other locations within the North Pole Refinery. In 1985 the facility owner installed a sulfolane extraction unit; this is the first known use of sulfolane in the refinery. Sulfolane is an industrial solvent used to remove the aromatics from the naptha during gasoline production. The chemical is listed as a high-production-volume chemical by the Organisation for Economic Cooperation and Development (OECD 2004).

Sulfolane has a low vapor pressure, suggesting it has low volatility; however, it is highly soluble in water (US EPA 2012). The chemical formula is $C_4H_8SO_2$ and the chemical structure is shown in Figure 1. A table of physicochemical properties is provided in Table 1.

Site characterization activities during 2000 to 2002 identified sulfolane in groundwater monitoring wells within the refinery boundaries. It is believed to come from leaks from the wastewater stream containing sulfolane, as well as fuel spills. Spills of pure sulfolane are also probable.

In 2004, ownership of the refinery changed and a Corrective Action Plan to address the fuel and sulfolane was submitted to ADEC. In 2006, ADEC set the groundwater cleanup level for sulfolane at 350 parts per billion (ppb), or 350 micrograms per liter (μg/L), based on available toxicity data and recommendations made for the Canadian Province of British Columbia (ADEC 2006).

Figure 1. Sulfolane Structure

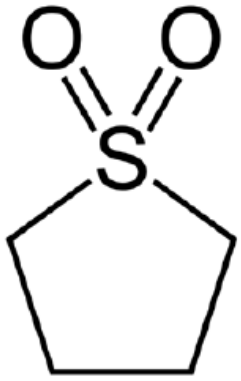

Table 1. Physicochemical Properties for Sulfolane (CASRN 126-33-0)

Property	Value	Source
Molecular weight	120.18	ATSDR 2010
Freezing point	27.4 – 27.8 °C	ATSDR 2010
Specific Gravity (30/20 °C)	1.265	ATSDR 2010
Vapor Pressure (27.6 °C)	0.0062 mm Hg	ATSDR 2010
Henry's Law constant	4.6×10^{-6} atm-m^3/mole	ATSDR 2010
Solubility in water (25 °C)	$\geq$100 g/L	OECD 2004

In 2009, new monitoring wells were installed at the northern edge of the refinery property as part of a review of system performance and overall monitoring program. These results indicated sulfolane concentrations higher than expected, although below 350 ppb. This finding led to additional sampling and ultimately the detection of sulfolane in the City of North Pole's public drinking water wells and in private drinking water wells down gradient of the refinery property. ADEC immediately contacted the Alaska Department of Health and Social Services (DHSS) to evaluate the potential public health risks from sulfolane. In February 2010, DHSS along with the Agency for Toxic Substances and Disease Registry (ATSDR) recommended that the drinking water action level be reduced to 25 ppb until more in-depth studies of sulfolane could be completed.

In a letter to FHRA, dated March 3, 2010, ADEC indicated that based on this new information related to sulfolane, the January 2002 Correction Action Plan was no longer sufficiently protective and ADEC set 25 ppb in groundwater as the interim sulfolane cleanup level at the site (ADEC 2010). ADEC directed FHRA to prepare a new site characterization work plan to address the current site conditions and directed FHRA to submit a Site Characterization Report and Revised Corrective Action Plan following the completion of the site characterization and prepare an Interim Removal Action Plan to address the light non-aqueous-phase liquid and sulfolane contaminated groundwater.

Also, in March of 2010, the ADEC's Contaminated Sites Program created a Technical Project Team to provide comprehensive and coordinated oversight for the investigation into the release of sulfolane at the FHRA refinery in North Pole. The team consists of experts in the fields of toxicology, engineering, hydrology, environmental chemistry and other relevant fields, working to ensure the protection of human health and the environment.

Site characterization activities in 2011 through 2013 continued to fill in data gaps by identifying areas on and off the refinery property necessary to assist with the long-term monitoring and evaluation of the sulfolane plume. For additional background on the site, please refer to ADEC's project website at http://dec.alaska.gov/spar/csp/sites/north-pole-refinery/.

1.2. Sulfolane Use at FHRA North Pole Refinery

Sulfolane is an industrial solvent used to extract aromatic compounds from hydrocarbon mixtures and to purify natural gas. At FHRA, sulfolane is used to extract aromatics from naptha to produce gasoline. In the aromatic extraction process, sulfolane is initially mixed with the petroleum feedstock (naphtha and light distillates). The sulfolane extracts the aromatics from the feedstock, and the aromatic-laden sulfolane is sent to a stripper for aromatic removal before returning to the extraction unit. Sulfolane as used in the refining process is dissolved in gasoline but it is more soluble in water, which allows it to dissolve in and be carried along with groundwater.

There are at least 150 similar extraction units in the United States. Sulfolane use in North Pole began in 1985. While gasoline was recently the only product that required the sulfolane extraction process, sulfolane may migrate into other FHRA products due to incidental carry over through the refinery's piping system. Fuels that may have contained sulfolane in the past include #1 fuel oil (jet fuel) and #2 fuel oil (diesel fuel). Only gasoline is monitored for sulfolane content as it is the only fuel produced at FHRA with a sulfolane specification (ADEC 2014).

1.3. Sulfolane in Private Drinking Water Wells

In 2009, sulfolane was detected in private wells downgradient of the North Pole Refinery. Since November 2009 through February 2014, groundwater samples have been collected from 640 private wells and analyzed for sulfolane (Barr Engineering Company 2014).

Alternative water solutions have been implemented for residents and businesses downgradient of the refinery whose drinking water wells have been impacted by sulfolane. The alternative water solution options include attachment to city water (for residents within the city limits), bottled water supply, bulk water tanks, or point of entry drinking water treatment systems. Through 2013, FHRA has provided 305 long-term alternative water solutions at 285 properties (note that some properties have more than one alternative solution). The long-term water solutions include 160 point of entry treatment systems, 113 bulk water tanks, and 32 long-term bottled water options (Barr Engineering Company 2014).

In addition to the long-term solutions described above, FHRA is currently providing interim bottled water to 223 residences that are either a) affected properties inside the plume that have not selected a long-term alternative water solution, b) have not had a detection of sulfolane, or c) are located within the buffer zone of the plume. FHRA has also provided 48 water tanks for use on gardens to affected properties that do not have a City water connection. In 2009, 28 residences were connected to City water (Barr Engineering Company 2014).

During the summer of 2010, a Gardening Sampling Project (Shannon and Wilson 2013) was conducted as a joint project with FHRA and DHSS to assess how garden produce that was watered with well water with various concentrations of sulfolane was affected. The study found that edible garden plants (fruits and vegetables) take up sulfolane. Sulfolane was found in at least one sample of all types of parts of plants that were sampled (leaves, fruits, flowers, stems and roots). DHSS found the detected sulfolane levels in the plants tested from these gardens were low, ranging from 8.4 milligrams per kilogram (mg/kg) in carrots (result was considered an estimated maximum possible concentration due to the presence of an interferent) to 198 mg/kg in beet leaves.

DHSS recommends North Pole gardeners use a water source that has no detectable level of sulfolane for growing edible plants, until more is known on the uptake of sulfolane into fruits and vegetables. North Pole residents with detectable levels of sulfolane in their well water have options for a long-term alternative water source for drinking and cooking purposes, in addition FHRA has offered to provide above-ground water tanks for residents to use for watering their gardens (DHSS 2012).

2. The Current Situation

The passage below is extracted from the ADEC web page (http://dec.alaska.gov/spar/csp/sites/north-pole-refinery/ accessed July 2014) and describes the current situation.

> On December 20, 2013, Flint Hills Resources Alaska filed a Request for an Adjudicatory Hearing to the Department of Environmental Conservation on Sulfolane. The [Alaska] DEC Commissioner responded on April 4, 2014, issuing an Order regarding Flint Hills' adjudicatory hearing request, vacating the SPAR[1] Division's decision that set the groundwater alternative cleanup level for sulfolane. The Commissioner remanded the cleanup level decision to the Division "for further development of the record and a decision on an approved alternative cleanup level..." The Commissioner is asking the Division to further consider and document the rationale, analysis, and data evaluation that leads to the Division's selection of a site-specific cleanup level for sulfolane.

[1] Spill Prevention and Response Division

> The Division is now undertaking the detailed analysis ordered by the Commissioner. A report containing an in-depth review of all the information and reevaluation of the cleanup level is anticipated to be delivered to the Commissioner before the end of the year. This report will document the Division's approved cleanup level for sulfolane.

The Division will consider the report from this peer review panel in their review of information and reevaluation of the cleanup level.

3. Toxicity and Key Studies

The toxicity of sulfolane has been reviewed and described in various publications (ATSDR 2010; US EPA 2012; CCME 2006). Sulfolane is rapidly absorbed via the oral and inhalation routes, but poorly absorbed via the dermal route of administration (Andersen *et al.* 1976; US EPA 2012). ATSDR indicated that the observed acute effects of sulfolane have included changes in thermoregulation, changes in motor activity, and changes in brain-wave patterns in rats (ATSDR 2010). Several sub-chronic studies (i.e., HLS 2001; Ministry of Health and Welfare Japan 1996, and as summarized in OECD 2004; Zhu *et al*. 1987), one 6-month chronic-duration study (Zhu *et al.* 1987), one developmental (Zhu *et al.* 1987), and one screening-level reproductive study (Ministry of Health and Welfare Japan 1999, and as summarized in OECD 2004) have evaluated the effects of animals orally exposed to sulfolane. No carcinogenicity studies of animals orally exposed to sulfolane have been identified in the literature (US EPA 2012). Two key studies, HLS 2001 and Zhu *et al*. 1987, have been used by various parties to develop oral RfDs for sulfolane. Those studies are discussed in more detail in this section.

3.1. Zhu *et al.*, 1987

Zhu *et al.* (1987) is a translated Chinese study. Zhu *et al.* (1987) conducted a series of studies on the acute toxicity of sulfolane in mice, white rats, and guinea pigs; subchronic (90-day) toxicity in white rats and guinea pigs; and chronic (6-month) oral toxicity in guinea pigs. Study authors also conducted a teratogenicity test and several genotoxicity tests (Ames, bone marrow micronucleus test, and sister chromatid exchange test) in mice. The studies were oral but the manner and schedule of administration was not specified (ATSDR 2011). In the 90-days study, sulfolane doses of 55.6, 167, and 500 milligrams per kilogram body weight per day (mg/kg-day) for 90 days were used. Decreased serum alkaline phosphatase activity was reported in rats at 500 mg/kg-day and decreases in serum alkaline phosphatase and white blood cell (WBC) counts were reported in guinea pigs at 55.6 mg/kg-day. In the chronic study, guinea pigs were exposed to 0.25, 2.5, 25, or 250 mg/kg-day of sulfolane for 6 months. Changes in histopathology of the white pulp of the spleen, liver and reduced bone marrow cell counts and serum chemistry changes were reported at concentrations of 2.5, 25 and 250 mg/kg-day.

3.2. Huntingdon Life Sciences, 2001

The Huntingdon Life Sciences Ltd. (HLS 2001) study involved exposure of male and female CD rats (10 animals per sex per dose group) to sulfolane in drinking water for 13 weeks at concentrations of 0, 25, 100, 400, and 1,600 milligrams per liter (mg/L). The study has been independently peer-reviewed by US EPA and has been found to follow Good Laboratory Practices (GLP; US EPA 2012). The study authors calculated actual dosages to be 2.1, 8.8, 35.0, and 131.7 mg/kg-day for males and 2.9, 10.6, 42.0, and 191.1 mg/kg-day for females. A comprehensive battery of observations were conducted, organ systems examined, and hematological examination, serum chemistry and urinalysis were performed. Study authors noted a clear reduction in lymphocytes, monocytes, and LUC counts in females given 100 mg/L (equivalent to 10.6 mg/kg-day) or more. Based on this endpoint, the study authors considered that the no observed effect level for this study is 2.9 mg/kg-day. There was no evidence of any chronic inflammatory change or comprised immune function. The authors indicated that the toxicological significance of the change in WBC is unclear.

4. Available Reference Doses for Review

In order to set a groundwater cleanup level, ADEC has tasked TERA with conducting an independent, expert peer review of the available chronic oral RfDs for sulfolane. Known chronic oral RfDs (or equivalent values) that are the subject of this review are provided in Table 2 and briefly discussed in this section. A summary of the uncertainty factors used in the development for each RfD are provided in Table 3. Appendix A includes an analysis by Gradient Corporation (Gradient) of the accuracy of the point of departure (PODs) derived using benchmark dose modeling. The analysis includes a comparison of existing PODs derived using benchmark dose modeling and consistency in modeling with US EPA guidelines and currently accepted scientific practices.

Table 2. Available Chronic Oral Reference Doses for Sulfolane

Source	Principal Study	Test Species	Endpoint	Modeling Approach	Point of Departure (mg/kg-day)	Composite Uncertainty Factor	Reference Dose (mg/kg-day)
CCME, 2006	HLS 2001	Rat (female)	WBC counts	NOAEL	NOAEL = 2.9	300	0.0097
ATSDR, 2010	Zhu *et al.* 1987	Guinea pig	Hepatic effects, changes in serum ALP, WBC counts	NOAEL	NOAEL = 0.25	100	0.0025
ATSDR, 2011	Zhu *et al.* 1987	Guinea pig	Dispersion of spleen white pulp	BMD	$BMDL_{10}$ = 1.5	1,000	0.002
TCEQ (Haney), 2011	HLS 2001	Rat (female)	WBC counts	BMD	$BMDL_{1SD}$ = 16.1 $BMDL_{HED}$[a] = 3.9	300	0.013
US EPA, 2012	HLS 2001	Rat (female)	WBC counts	NOAEL	NOAEL = 2.9	3,000	0.001
Magee, 2012	HLS 2001	Rat (female)	WBC counts	BMD	BMDL = 11.64	1,000	0.01
Thompson *et al.*, 2013	HLS 2001	Rat (female)	WBC counts	BMD	$BMDL_{1SD}$ = 16 $BMDL_{HED}$[a] = 3.9	300	0.01
Health Canada, 2014	HLS 2001	Rat (female)	Lymphocytes	BMD	$BMDL_{1SD}$ = 4.12	1,000	0.00412

Notes:
BMD = benchmark dose
BMDL = benchmark dose limit
NOAEL = no observed adverse effects level
WBC = white blood cell
(a) – The HEDs (human equivalent doses) were derived using a species scaling adjustment factor of ¾ body weight.

Table 3. Summary of Uncertainty Factors[a]

Source (By Date)	UF_A	UF_D	UF_H	UF_L	UF_S	UF_C
CCME, 2006	10	3[b]	10	--	--	300
ATSDR 2010	10	--	10	--	--	100
ATSDR, 2011	10	--	10	--	10	1,000
TCEQ (Haney), 2011	--	3	10	--	10	300
US EPA, 2012	10	3	10	1	10	3,000
Magee, 2012	10	--	10	--	10	1,000
Thompson *et al.*, 2013	3	3	3	--	10	300
Health Canada, 2014	10	10	10	--	--	1,000

Notes:

-- = no value provided
UF_A = animal to human uncertainty factor
UF_D = incomplete-to-complete database uncertainty factor
UF_H = intrahuman uncertainty factor
UF_L = LOAEL-to-NOAEL uncertainty factor
UF_S = subchronic-to-chronic uncertainty factor
UF_C = composite uncertainty factor

(a) Uncertainty factors are not defined by all groups using the same nomenclature. The uncertainty factors were categorized based on most appropriate descriptor based on the intent of each factor under US EPA method.

(b) Based on the CCME application of uncertainty factors, this value was used to account for adequate, but not extensive dataset; subchronic-chronic extrapolation; and serious effects concerns (CCME 2006).

4.1. CCME, 2006

In 2006, Canadian Council of Ministers of the Environment (CCME) developed a tolerable daily intake (TDI) for sulfolane as part of establishing a soil guideline. Three chronic or subchronic studies for sulfolane were reviewed: Andersen *et al.* (1977), Zhu *et al.* (1987) and HLS (2001). The TDI of 0.0097 mg/kg-day was based on the HLS 2001 study. CCME indicated that they did not use the Zhu *et al.* (1987) study due to uncertainties in the interpretation of some of the toxicological endpoints and the lack of data available to confirm that "good laboratory practice" had been followed. The HLS study was also preferred over Andersen *et al.* (1977) due to a more applicable route of administration (oral versus inhalation). The no observed adverse effects level (NOAEL) in female rats in the HLS (2001) study was 2.9 mg/kg-day based on a reduction in WBC counts. A 300-fold composite uncertainty factor (UF) was applied to account for interspecies differences (10-fold), variability in human sensitivity (10-fold), and adequate, but not extensive dataset, subchronic-to-chronic extrapolation, serious effects concerns (3-fold) (CCME 2006).

4.2. ATSDR, 2010 and 2011

In 2010, the Alaska DHSS requested that the ATSDR Division of Toxicology and Environmental Medicine provide a chemical specific health consultation for the chemical sulfolane. In making their recommendations for drinking water consumption, ATSDR selected a sub-chronic oral NOAEL of 0.25 mg/kg-day from a study in guinea pigs (Zhu *et al.* 1987). ATSDR applied a 100-fold UF to account for extrapolation from animals to humans (10-fold) and human variability (10-fold). ATSDR recommended that human exposures be limited to no more than 0.0025 mg/kg-day or 25 ppb for infants, 40 ppb for children and 87.5 ppb for adults (ATSDR 2010). These levels were used by ADEC to set an interim groundwater cleanup level of 25 ppb, the most conservative health advisory level (ADEC 2010).

In 2011, ToxStrategies Inc., LLC (ToxStrategies) expressed concern about the methodology ATSDR employed in setting the action level for sulfolane and ToxStrategies criticized ATSDR for not having done an independent dose-response analysis of the key study and for using semi-quantitative methods to derive its public health action level. ATSDR, as a matter of policy, re-examined its decisions in the event that compelling new evidence or reasoning is presented (ATSDR 2011).

ATSDR revised their 2010 Health Consultation in 2011 and utilized benchmark dose (BMD) modeling, which resulted in an altered recommended public health action levels. ATSDR noted that they selected the Zhu *et al.* (1987) study for the derivation of the public health action level because it was conducted for the longest period of time (twice the duration of the HLS study). Another advantage of the Zhu *et al.* study was that it was available in the peer-reviewed literature. The HLS study had not been peer-reviewed at the time of the ATSDR Health Consultation. ATSDR used US EPA's Benchmark Dose Software (BMDS) to establish benchmark dose lower bound 95% confidence intervals (BMDLs) for each of the studies and their health effects including the following: Zhu *et al.* liver, Zhu *et al.* spleen (3 months), Zhu *et al.* spleen (6 months), HLS WBC (using both historical and concurrent controls), HLS

lymphocytes (historical and concurrent controls), OECD live pups, and OECD birth index. The most sensitive POD was shown to be a BMDL for dispersion of the white pulp of the spleen from Zhu *et al.* at 1.5 mg/kg-day in the guinea pig. ATSDR recommended a composite UF of 1,000-fold (10-fold for animal to human extrapolation, 10-fold for variability in human sensitivity, and 10-fold for extrapolation of an intermediate dose to a chronic dose), resulting in a sulfolane action level of 0.002 mg/kg-day (ATSDR 2011).

4.3. Texas Commission on Environmental Quality, 2011

In 2011, the Texas Commission on Environmental Quality (TCEQ) set a chronic oral RfD of 0.013 mg/kg-day based on a proposal from ToxStrategies. TCEQ adopted the POD proposed by ToxStrategies of 3.9 mg/kg-day for decreased WBC count. The POD was based on a BMDL of 16.1 mg/kg-day and the corresponding body weight scaling to calculate a human equivalent dose. TCEQ applied a composite UF of 300-fold based on 3-fold for database uncertainty, 10-fold for use of a subchronic study, and 10-fold for intrahuman variability. TCEQ believed the body weight scaling adequately accounted for animal-to-human extrapolation without use of an additional uncertainty factor (Haney 2011).

4.4. United States Environmental Protection Agency, 2012

In 2011, ADEC requested that the US EPA review available literature on sulfolane toxicity as part of the Provisional Peer-Reviewed Toxicity Value (PPRTV) program. The US EPA found the most acceptable study to use for deriving an oral RfD is the GLP compliant study conducted by HLS (2001) that identified reduced WBC counts in female rats exposed to sulfolane in drinking water for 13 weeks. The HLS study showed kidneys and WBC as targets of toxicity following exposure of rats via drinking water for 13 weeks. The critical endpoint, decreased total and differential WBC count (lymphocytes, basophils, monocytes, and large unstained cell [LUC] counts) in female rats, was chosen as the basis for the point of departure. US EPA had the HLS study independently peer reviewed by three scientific experts in the summer of 2011 (US EPA 2012).

The US EPA attempted BMD modeling of total WBC count in female rats using the available continuous models (polynomial, power, Hill, linear) in US EPA's BMD software (Version 2.1.2) in a manner consistent with US EPA's BMD technical guidance (US EPA 2000). A BMR of one standard deviation change from the control mean was selected in the absence of a biological rationale for using an alternative BMR. The BMD analysis resulted in significant lack of fit (goodness-of-fit $p < 0.10$) for all continuous models employing nonconstant (modeled) variance. The homogeneity variance p-value of less than <0.1 indicates that nonconstant variance is the appropriate variance model (and therefore it is inappropriate to assume constant variance for these data).

Because these data were not amenable to BMD modeling, US EPA employed a NOAEL approach to identify the POD. The leukocyte data indicate a consistently observed effect, and US EPA identified a NOAEL of 2.9 mg/kg-day in females to use as the POD for deriving the oral chronic RfD. No dosimetric adjustments were made because sulfolane was administered

continuously via drinking water, and the principal study authors' calculated average daily dose based on body weight and drinking water consumption data. A composite uncertainty factor of 3,000 was applied to the NOAEL, resulting in a chronic, oral reference dose of 0.001 mg/kg-day. The UFs applied include 10-fold for interspecies extrapolation, 10-fold for intraspecies differences, 10-fold because a subchronic study was used, and a 3-fold factor for database because there is an acceptable developmental study in mice (Zhu *et al.* 1987) but only a screening-level one-generation reproduction study in rats (Ministry of Health and Welfare Japan 1999 and as summarized in OECD 2004) via the oral route.

4.5. Magee, 2012

In 2012 ARCADIS, a FHRA contractor, submitted to ADEC as part of the site-specific human health risk assessment, an evaluation of existing RfDs for sulfolane and derived an RfD of 0.01 mg/kg-day (Magee 2012). The ARCADIS RfD used the WBC count reduction from the HLS (2001) study as the critical endpoint and utilized BMD modeling with log transformed data. Historical control variances were used in the model. A POD of 11.64 mg/kg-day was chosen and a composite UF of 1,000 was used (10-fold for interspecies uncertainty; 10-fold for intraspecies uncertainty; and 10-fold for subchronic-to-chronic exposures) (Magee 2012). In 2014, FHRA submitted to ADEC a supplement to the site human health risk assessment proposing an updated toxicity value for sulfolane based on the Thompson *et al.* (2013) article (Perkins Coie 2014; ARCADIS 2014).

4.6. Thompson *et al.*, 2013

In 2012, ToxStrategies scientists published a chronic noncancer oral RfD for sulfolane (Thompson *et al.* 2013). Thompson *et al.* modeled WBC effects, total WBC, lymphocyte, monocytes and LUCs cell count data endpoint using the US EPA BMDS. None of the models in the BMDS were able to reasonably fit the data. The authors then log-transformed the data and reran the BMDS model. Historical control hematology data was used from female rats from HLS (2001) to provide the data to estimate a BMDL based on the control standard deviation. The authors determined that the linear, power, polynomial and exponential models all provided reasonable fits to the data. To be consistent with the US EPA benzene assessment, the linear model was chosen for WBC and lymphocyte modeling results. The resulting POD of 16 mg/kg-day was chosen. The authors indicated that since there were no published toxicokinetic models for sulfolane, human equivalent dose (HED) values were calculated using allometric scaling resulting in a POD_{HED} of 3.9 mg/kg-day. A composite UF of 300 was applied to the POD based on 3-fold UF to account for interspecies sensitivity because allometric scaling was used, 3-fold for intraspecies uncertainty because effects on WBC counts were only observed in female rats, 10-fold for use of a subchronic study, and 3-fold for database uncertainties based on lack of a two-generation reproduction/developmental study (Thompson *et al.* 2013). Thompson *et al.* (2013) derived a chronic RfD of 0.01 mg/kg-day.

4.7. Health Canada, 2014

Health Canada established a Drinking Water Guidance Value at the request of the Alberta Department of Environment and Sustainable Resource Development in 2014 (Health Canada 2014). Health Canada utilized the BMD modeling conducted by ATSDR (2011) based on the HLS (2001) study to derive a TDI. BMD modeling of total WBC and lymphocyte counts using historical and concurrent control HLS (2001) datasets from female rats resulted in a BMDL at one standard deviation of 4.12 mg/kg-day which was used as the POD. A composite UF of 1,000 was applied: 10-fold to account for interspecies variability, 10-fold for intraspecies variability, and 10-fold for database deficiencies to account for use of a subchronic study and lack of appropriate toxicity and epidemiological studies. The final TDI was set at 0.00412 mg/kg-day (Health Canada 2014).

5. National Toxicology Program Sulfolane Toxicity Studies

The National Toxicology Program (NTP) Board of Scientific Counselors' endorsed sulfolane nomination at its board meeting in December 2011 (NTP 2011b). The specific aims of the NTP work include the following:

1. Evaluate rodent species sensitivities in short-term i*n vivo* assays via an oral route of exposure, which would include an evaluation of immunotoxicity in adult animals.
2. Evaluate the route of exposure influence on internal dose, tissue distribution, in order to relate to potential toxicity and improve the toxicokinetic and absorption, distribution, metabolism, and excretion data set for sulfolane.
3. Evaluate potential reproductive and developmental toxicity, developmental immune and neurotoxicity, chronic toxicity, and carcinogenic activity. (NTP 2011a)

As part of the evaluation, NTP is taking a tiered approach[2]. First, short term animal studies have been conducted to examine potential differential rodent species sensitivities (mice vs. rat vs. guinea pig), which will be used to inform future toxicity, kinetic, and absorption, distribution, metabolism, and excretion studies. Second, toxicokinetic and absorption, distribution, metabolism, and excretion studies in different rodent species will evaluate species and potentially route influence on these parameters. In addition, sulfolane will be evaluated for reproductive, developmental, developmental neuro- and immune-toxicity, potentially in an oral exposure modified one-generation study that incorporates *in utero* and lactational exposure followed by an evaluation of these various toxicities in the offspring. Third, the toxicity and carcinogenic activity of sulfolane will be evaluated in a chronic exposure study using a drinking water route of exposure (NTP 2011a).

Under the direction of Dr. Chad Blystone, a toxicologist and the sulfolane project leader with the National Institute of Environmental Health Sciences/Division of the NTP, laboratory research

[2] Note completion of all of the NTP studies is subject to a number things including secured funding.

began earlier this year. The work is being conducted in partnership with the National Institute for Occupational Safety and Health.

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APPENDIX A - Review and Verification of Existing Sulfolane Dose-Response Assessments