NTP Research Concept: Sulfolane

Project Leader

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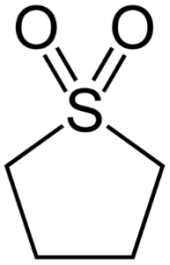

Background and Rationale

Sulfolane (CAS# 126-33-0) was nominated by the State of Alaska's Department of Environmental Conservation and Department of Health and Social Services, Mayor of the Fairbanks North Star Borough, Alaska, a Senator from the Alaska State Legislature, and the Agency for Toxic Substances and Disease Registry.

Sulfolane is a polar solvent primarily used in the refining of natural gas and petroleum. Other uses include fractionalization of wood tars and curing of epoxy resins. Production of sulfolane was between 10 and 50 million pounds in the United States according the US EPA's 2006 Inventory Update Rule reporting.

Recently sulfolane has been detected in well water within the town of North Pole, Alaska. A plume was identified in groundwater, originating from a petroleum refinery, and the highest concentration measured in wells outside the refinery was 269 ppb as of January 2011. Due to the contamination, residents were being provided bottled water for use and additional wells were created outside the plume area. Sulfolane contamination has also been identified within Canada in areas near sites of natural gas or petroleum refining and may be present as a groundwater contaminant near other sites of refining around the county. A few studies have demonstrated the uptake of sulfolane into vegetation at contaminated sites. In an occupational setting, inhalation and dermal contact could be the primary route(s) of exposure.

Animal toxicity data for sulfolane are limited. An inhalation study of aerosolized sulfolane investigated potential toxic effects in various species (rats, guinea pigs, dogs, squirrel monkeys), but experimental detail and design are limited (*1*). A Chinese study describing a 90-day (rat and guinea pig), 6-month (guinea pig), and prenatal toxicity study (mice) using an oral route of exposure suggested that guinea pigs are a more sensitive species as compared to rats based on reductions in leukocyte numbers, but experimental detail and data were lacking in the translated report (*2*). Toxicokinetic studies of sulfolane are also limited, but suggest that it has a short half-life, distributes widely to tissues throughout the body including the brain, and that maternal transfer occurs during gestation (*3, 4*).

A screening reproductive study (OECD 421) in rats suggests that sulfolane exposure induces reproductive toxicity (e.g., reduction in litter size, pup weights), but a comprehensive reproductive study has not been conducted. Neurotoxicity (convulsions, seizures, hyper/hypoactivity) has also been observed in the inhalation and toxicokinetic

studies mentioned above and some acute sulfolane exposure studies via an intraperitoneal route (*3*-*5*).

A 13-week exposure study that exposed young adult rats to drinking water containing sulfolane and included a neurotoxicity evaluation provides the greatest amount of experimental detail and data (*6*). In this study, males were reported to have increased incidence of hyaline droplets and granular casts within the kidneys, which were attributed to the male rat specific alpha-2u mechanism by the authors. The most sensitive endpoint identified was a reduction in white blood cell counts in female rats, which is consistent with previous reports.

A chronic toxicity and carcinogenicity evaluation of sulfolane has not been conducted. Sulfolane was negative in genotoxicity assays. 3-sulfolene, an intermediary in the production of sulfolane, was evaluated for carcinogenic activity by NCI and no increase in tumor incidence was reported. However, the high dose in this two-dose study had dramatic effects on survival in rats and mice, males and females. There were some increases in tumor incidence in the low dose group, but interpretation is difficult due to having a single dose evaluation.

Together, these studies suggest that sulfolane may target the immune, nervous, and reproductive systems. There is a suggestion that the most sensitive species may be guinea pigs, but it is difficult to determine at this time since the data from the 90-day and 6-month study are poorly reported. An evaluation of developmental effects (immune, neurological, reproductive) after a gestational and lactational exposure is lacking. Furthermore, there is a lack of an adequate evaluation of toxicity following chronic exposure.

Currently there are no human data for exposure or possible health effects. The state of Alaska Department of Health and Social Services reviewed cancer and birth defect rates in the area and did not find any unusually high incidences. At this time, no human health studies are planned by the state. The small population of North Pole, Alaska (< 2000), inadequate information to reconstruct past exposure, probable short half-life of the chemical, and likely co-exposure to other chemicals from refining creates large obstacles to attributing any adverse health outcomes to sulfolane exposure.

Key Issues

1. A key issue in evaluating sulfolane toxicity is characterizing species differences in response to exposure. Suggestive evidence, although poorly reported, points to guinea pigs being more sensitive than rats to sulfolane. In addition to species differences, sex differences would need to be evaluated. Previous studies suggest that the immune system is more sensitive in females than males.

2. In conjunction to the issue above, understanding species differences in sulfolane kinetics, metabolism, distribution, and metabolism is needed. Furthermore, route specific kinetics and tissue distribution of sulfolane needs to be improved.

3. A lack of data for human exposure and potential health outcomes coupled with logistical challenges are another key issue.

Specific Aims

1. Evaluate rodent species sensitivities in short-term *in 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 ADME data set for sulfolane.

3. Evaluate potential reproductive and developmental toxicity, developmental immune and neurotoxicity, chronic toxicity, and carcinogenic activity.

Proposed Approach

In addressing the challenges of evaluating sulfolane toxicity, a tiered approach will be used. First, short term animal studies will examine potential differential rodent species sensitivities (mice vs. rat vs. guinea pig), which will be used to inform future toxicity, kinetic, and ADME studies. As part of this evaluation, an adult immunotoxicology study would be used to evaluate species and gender differences.

Second, toxicokinetic and ADME studies in different rodent species will evaluate species and potentially route influence on these parameters. These studies could help bridge internal dose estimates between inhalation (likely occupational exposure) and oral exposure toxicity (water contaminant exposure) studies. 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.

Due to the large obstacles outlined above, we will discuss with Federal partners the opportunities for and priority of evaluating sulfolane exposure and health outcomes in the human population. We are currently exploring with NIOSH the feasibility of conducting an occupational exposure study, in order to assess the scope and magnitude of sulfolane exposure in different workplace scenarios.

Significance and Expected Outcome

Sulfolane is a high production chemical with known human exposure in Alaska and potentially in other areas of gas and petroleum refining. The studies outlined in this research concept will address the uncertainties (e.g., species sensitivities) and general lack of data for evaluating sulfolane toxicity. By incorporating an assessment of rodent species sensitivities, influence of route on internal dose, and incorporating a developmental exposure, these studies will provide much needed data for improved sulfolane risk assessments. Furthermore, the findings from the experimental toxicology studies will guide the design of potential human studies by identifying relevant adverse outcomes to evaluate and informing appropriate methods for assessing exposure.

References

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