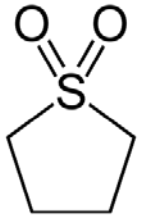
NTP
National Toxicology Program

Sulfolane



Chad Blystone, Ph.D., D.A.B.T.
National Institute of Environmental Health Sciences

NTP Board of Scientific Counselors Meeting
December 15, 2011

National Institute of Environmental Health Sciences / National Institutes of Health
National Institute for Occupational Safety and Health / Centers for Disease Control
National Center for Toxicological Research / Food and Drug Administration

Nomination and Use

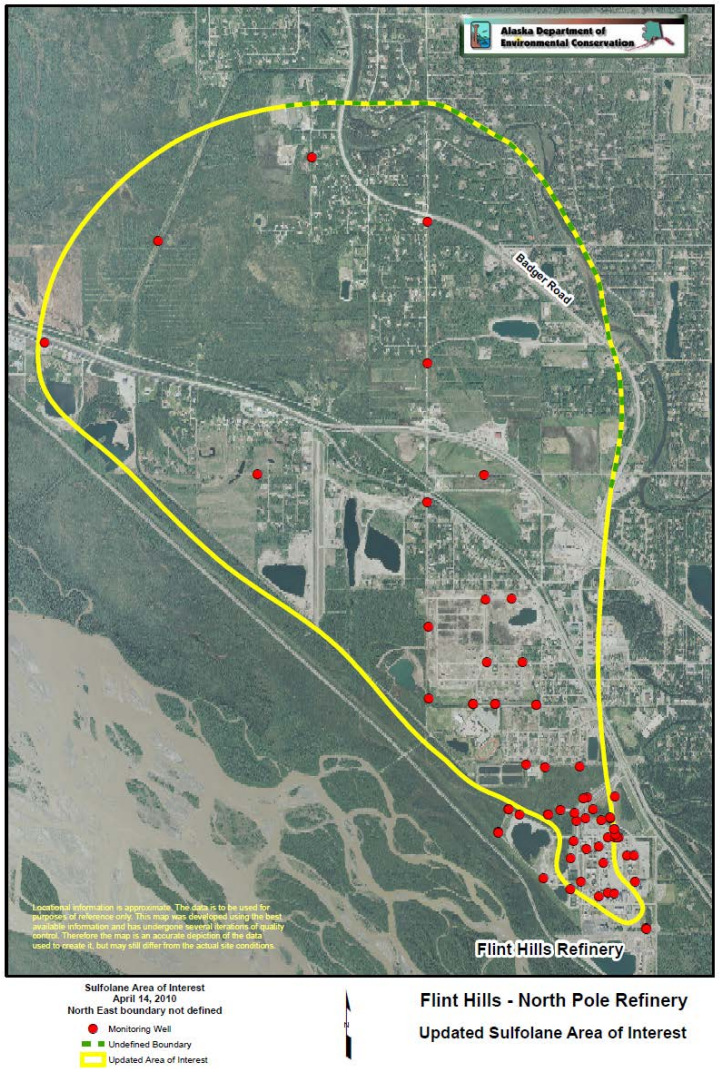
- Sulfolane was nominated by Alaska's Department of Environmental Conservation with support from Alaska's Department of Health and Social Services, the Mayor of Fairbanks North Star Borough, Senator from the State Legislature, and Agency for Toxic Substances and Disease Registry (ATSDR)
  - Concern over insufficient sulfolane developmental and chronic toxicity data
- Sulfolane is a solvent that is primarily used in natural gas/petroleum refining. Other uses include fractionalization of wood tars, curing agent in epoxy resins, and in production of electronics and polymers
- US production of sulfolane in 2006 was between 10 - 50 million pounds (US EPA IUR).

Sulfolane Exposure

- Sulfolane is a highly polar chemical with a low vapor pressure and is miscible in water
- Presumed not to break down easily in groundwater due to low oxygen and nutrients. It does not accumulate in aquatic food chain, but is taken up by plants
- Occupational exposure may by through inhalation
- Groundwater in North Pole, Alaska is contaminated with sulfolane and it is present in other sites within Canada

Sulfolane Well Concentrations in North Pole, Alaska

- Detected in nearly 300 drinking water wells
- Refinery offering other sources of water
- Exposure may be up to ~20 years



http://dec.alaska.gov/spar/csp/sites/north-pole-refinery/docs/maps/npr-plume-2010-4-14-small.pdf

Sulfolane Animal Studies

- Sulfolane toxicokinetic (TK) studies are limited, but suggest a short half life, placental transfer, and large volume of distribution

- Some studies observe neurotoxicity: convulsions/seizures, hyper/hypo-activity, hypothermia

- Primary toxicity studies to date:
  - Subchronic Inhalation (Anderson et al., 1977)
  - Subchronic, 6-month, prenatal developmental toxicity (Zhu et al., 1987)
  - OECD 421, 28-day toxicity (Ministry of Health, Japan 1996/1999)
  - Subchronic drinking water (HLS 2001 sponsored by Shell Canada Ltd)

Sulfolane Inhalation Study

- Inhalation studies of aerosolized sulfolane (3% water) in rats, guinea pigs, dogs, and squirrel monkeys:
  - 37 days 495 mg/m^3 8/hr day, 5d/wk
    - Mortality in monkeys
    - Chronic lung inflammation (all animals); chronic liver inflammation (rats)
  - 90 days (roughly) 23hr/day, 7 days/wk, 2.8, 4.0, 20, 160, 200 mg/m^3
    - Decreased white blood cells and increased fatty liver in guinea pigs at high dose
    - Mortality in dogs and monkeys at high dose
  - Authors identify NOAEL = 20 mg/m^3

Sulfolane Toxicity Data

- 28-day exposure to rats (0, 60, 200, 700 mg/kg):
  - Weight loss and reduced food consumption (males; females recovered)
  - Increased hyaline droplet incidence in kidneys (males) and decreased erythrocytes in females
- 90-day oral exposure to rats and guinea pigs (0, 55.6, 167, 500 mg/kg):
  - Rat: clinical chemistry changes at top dose
  - Guinea pig: white blood cells decreased in all dose groups
- 6-month exposure to guinea pigs (0, 0.25, 2.5, 25, 250 mg/kg):
  - 3-month interim: clinical chemistry, low marrow cell number, splenic white pulp shrinkage
  - 6-month: fatty liver, splenic white pulp shrinkage
  - NOAEL = 0.25 mg/kg

Sulfolane Subchronic Toxicity Data (HLS 2001)

- 13-week rat drinking water study:
  - Food and water consumption unaffected
  - FOB tests were negative
  - Reduced white blood cell counts in females
  - No organ weight changes, but hyaline droplets increased in male kidneys

- NOEL 100 mg/L (8.8 mg/kg/d) for males and 25 mg/L (2.9 mg/kg/d) for females

Sulfolane Reproductive and Developmental Toxicity Data

- OECD 421: SD rats dosed 14 days prior to mating to PND 3
  - Reduced body weights and some mortality at top dose
  - Reduce estrous cycles, increased litter loss, decreased number of pups, low pup weight at top dose
  - Decreased birth index and number of pups on PND 0 and 4 at mid dose

- Prenatal developmental toxicity in mice:
  - Fetal resorptions and some skeletal abnormalities in top dose

Chronic Toxicity Data

- Sulfolane has not been tested for chronic toxicity and carcinogenic activity
- Sulfolane genotoxic assays are mostly negative (in vitro/in vivo)
- 3-Sulfolene, an intermediate in the production of Sulfolane, was tested (NCI 1978; NTP Technical Report #102)
  - Tumor incidence was not attributed to 3-Sulfolene exposure
  - Survival was poor in both rats and mice in this two-dose study

Sulfolane Human Health Effects

- Sulfolane exposure and human health effects have not been characterized
  - State of Alaska is reviewing cancer and birth defect rates
- Epidemiology studies for North Pole, Alaska have challenges:
  - Small population of < 2000 (low power)
  - Past exposure unknown and not easily reconstructed
  - Possible short half life of chemical
  - Co-exposure to other chemicals
- ATSDR Reviewed Toxicity Data (2010, 2011) and US EPA developing Provisional Peer Review Toxicity Value

Key Issues

- Species differences in response to exposure: limited evidence suggests guinea pigs are more sensitive than rats
- Understanding sex differences: previous studies suggest that the immune system is more sensitive in females than males.
- 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.
- A lack of data for human exposure and potential health outcomes coupled with logistical challenges

Specific Aims and Proposed Approach

- First, 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.
  - Mice vs Rats vs Guinea Pigs
  - Sulfolane was included in the 10,000 chemicals going forward in Tox21

Specific Aims and Proposed Approach

- Evaluate the route of exposure influence on internal dose, tissue distribution, in order to relate to potential toxicity and improve the TK and ADME data set for sulfolane.
  - ADME and TK studies in sensitive species and compare males and females

Specific Aims and Proposed Approach

- Evaluate potential reproductive and developmental toxicity, developmental immune and neurotoxicity, chronic toxicity, and carcinogenic activity.
  - Modified One Generation study with additional cohorts (e.g. neurotoxicity)
  - Chronic toxicity and carcinogenicity study
- Discussing with NIOSH the possibility of an occupational exposure study

Significance and Expected Outcome

- Address the uncertainties (e.g. species sensitivities) and lack of developmental and chronic toxicity data for evaluating sulfolane toxicity

- 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 sulfolane risk assessment.