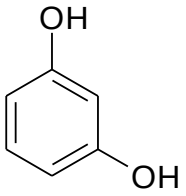
SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	108-46-3
Chemical Names	Resorcinol (1,3-Benzenediol)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

The melting point of resorcinol ranges between 109-111°C and the boiling point ranges between 276.3 - 277 °C at 1013 hPa. The vapor pressure is 0.00065 hPa at 25ºC. The water solubility of resorcinol is 717 g/L and the log Kow is 0.8 at 25°C.

Human Health

Toxicokinetic studies in rats and rabbits suggest that orally-administered resorcinol is rapidly absorbed, metabolized and excreted in the urine primarily as a monoglucuronide conjugate. Minor metabolites included a monosulphate conjugate, a mixed sulfate-glucuronide conjugate, and a diglucuronide conjugate. Rats given repeated oral doses of resorcinol appeared to increase the rate of metabolism. Dermal absorption of resorcinol is slow in humans but shows the same urinary excretion pathway and metabolites as those in orally treated rats and rabbits.

Following OECD TG 401, the acute oral LD_{50} of resorcinol in rats is 510 mg/kg bw. Clinical signs of toxicity included ptosis, respiratory effects, lethargy, abnormal gait, tremors, convulsions and salivation. An additional acute oral toxicity study in rats resulted in an LD_{50} of 980 mg/kg bw. Hyperemia and distention of stomach and intestines were observed in the animals that died. In rats exposed by inhalation to an aerosol of resorcinol, the 1-hr and 8-hr LC_0 values were $\geq$ 7800 mg/m^3 and 2800 mg/m^3, respectively. No lesions attributable to inhalation of the aerosol were seen at gross necropsy. The rabbit 24 hour dermal LD_{50} was 3360 and 2830 mg/kg bw, for flaked and industrial grade resorcinol, respectively. Both grades produced necrosis of the skin; clinical signs included salivation, tremors, and convulsions prior to death. The overt CNS effects were considered to be associated with bolus dosing.

In an OECD TG 404 study, resorcinol was not a skin irritant when applied to the skin of rabbits. In a study conducted similar to OECD test guideline 405, resorcinol was not considered an eye irritant in rabbits when applied at a concentration of 2.5% in water. In additional studies, resorcinol was found to be slightly to severely irritating to the skin and severely irritating to eyes when administered in a dissolved and semi-solid state. In an OECD TG 406 study, resorcinol was a moderate skin sensitizer in guinea pigs. In two separate studies following OECD TG 429, resorcinol was determined to be a weak skin sensitizer in mice. Resorcinol has elicited allergic skin reactions in patch tests carried out on dermatitis patients.

An OECD TG 408 study was performed with male and female rats receiving 0, 40, 80 or 250 mg/kg

bw/day via oral gavage 5 days/week for 90 days. At 250 mg/kg bw/day, intermittent convulsive movements and excessive salivation were observed along with loud breathing in two males, one during week 6 and the other between weeks 11 and 13. However, the functional observational battery did not reveal any treatment related neurological effects. Female animals receiving 250 mg/kg/day from week 4 to 8 showed reduced body weight gains. The NOAEL for both sexes was 80 mg/kg/day.

A series of studies was conducted by NTP in rats and mice at 17 days, 13 and 104 weeks. The lowest NOAEL reported in rats was in the 17 day study oral bolus (gavage) study and was 27.5 mg/kg bw (females) based on overt CNS effects at doses of 55 mg/kg bw and higher. The lowest LOAEL in rats was identified in the 104 week study with a LOAEL = 112 mg/kg bw (males) based on overt CNS effects at all doses, body weight changes (decreased) and increased mortality at the highest dose of 225 mg/kg bw. In the 13-week study increased absolute and relative liver weights were seen in females and males at 65 and 130 mg/kg bw, respectively. In addition, absolute and relative adrenal gland weights were significantly increased in all surviving male dosed groups.

In the NTP studies, the lowest NOAEL reported in mice was in the 17-day study at 75 mg/kg bw/day based on overt CNS effects in males at 150 mg/kg bw/day. The lowest LOAEL in mice was identified in the 104 week study at 112 mg/kg bw/day based on overt CNS effects (in both sexes) at 112 and 225 mg/kg bw/day. As with the rats, acute CNS effects were observed in mice. An NTP review panel concluded that the overt CNS effects seen in the NTP studies were an acute response to treatment. The dosing method (bolus) was probably a key factor, since no CNS effects were seen when similar or higher doses were given via the drinking water. Decreased adrenal gland weights were reported for male mice in the 13 wk gavage study only while increased adrenal gland weights were reported in male rats. The significance of the adrenal and liver weight changes remains unclear as neither effect were reproduced in the 104 week and subsequent studies.

Acute CNS effects, adrenal weight changes and liver weight changes reported in the 17-day and 13-week studies in rats and mice were not observed in a subsequent reproduction drinking water study (OECD TG 416) conducted in rats at concentrations up to 3000 mg/L. Mean cumulative body weights were decreased in the 3000 mg/L group in both sexes and generations. The NOAEL was considered to be 3000 mg/L for parental systemic and offspring toxicity (ca. 233 mg/kg/day (males), 304 mg/kg/day (females (during premating and gestation)), 660 mg/kg/day (females (during lactation)). This study also included a detailed evaluation of the thyroid endpoints. No significant effects on the thyroid were observed in rats given up to 233 mg/kg bw/day (males) or 304 mg/kg bw/day (females).

Given the weight of evidence from the above repeated dose studies, the lowest value associated with a reproducible effect (reduced body weight) was 250 mg/kg/day resulting in a NOAEL = 80 mg/kg/day.

Resorcinol generally showed no evidence of activity in Ames bacterial mutation assays. In mammalian cells in culture, it induced chromosome aberrations (breaks and micronuclei), but no SCE effects. In an *in vitro* Unscheduled DNA Synthesis Assay in rat hepatocytes, resorcinol was negative. In an OECD TG 476 (*in vitro* thymidine kinase locus) study, resorcinol was positive without activation in the L5178Y mouse lymphoma cells; however, this result was probably due to chromosome aberrations (induction of small colony mutants), not mutagenicity. In an OECD TG 487 (*in vitro* Micronucleus assay) study, resorcinol was positive with and without activation in female human lymphocytes. In an *in vitro* hamster embryo cell morphological transformation assay following OECD guidelines, resorcinol was negative. Resorcinol was negative for inducing micronuclei in six *in vivo* micronucleus assays in which one study was conducted following OECD TG 474. In one of two NTP *in vivo* micronucleus assays, resorcinol was positive for inducing micronuclei. In a transgenic mouse model, resorcinol was negative for activating RasH2. In studies to evaluate the effectiveness of the transgenic mouse model, resorcinol was negative in p53+/- while positive in Tg.AC. Based on the weight of evidence, resorcinol appears to induce chromosome aberrations *in vitro* but not *in vivo*.

No evidence of carcinogenic activity was seen in studies conducted according to US EPA/FDA guidelines where rats and mice were given resorcinol by gavage on 5 days/week for 2 years.

In an OECD TG 416 study, rats (30/sex/group) were exposed to resorcinol via drinking water for at least 70 days prior to mating. Resorcinol concentrations were 0, 120, 360, 1000 or 3000 mg/L water for both the F0 and F1 generations. On a body weight basis (average F0 and F1 animals), the

concentrations corresponded to resorcinol intakes of approximately: 0, 11, 31, 86 or 233 mg/kg bw/day for males over the entire generational span; 0, 16, 48, 126 or 304 mg/kg bw/day for females during pre-mating and gestation; and 0, 28, 85, 225 or 660 mg/kg bw/day for females during lactation, respectively. Reproductive performance and spermatogenic endpoints were unaffected by resorcinol. No treatment-related effects were observed on F1 and F2 pup survival, macroscopic findings or effects on organ weights. Mean cumulative body weights were decreased in the 3000 mg/L groups in both sexes and associated with decreased water consumption.

The NOAEL for male reproductive toxicity was determined to be 3000 mg resorcinol/L (ca. 233 mg/kg bw/day). The maternal NOAEL was 3000 mg/L (304 mg/kg bw/day during premating and gestation and 660 mg/kg/day during lactation). The NOAEL for reproductive toxicity (fertility and development) was 3000 mg/L which corresponds to 245 mg/kg bw (males) and 295 mg/kg bw (females) in the F1 generation.

In an OECD TG 414 study, female rats (24/group) were exposed to resorcinol via oral bolus dosing (gavage) from days 6 – 19 of gestation at 0, 40, 80 or 250 mg/kg bw/day. The maternal and developmental NOAELs were 80 (based on statistically significant decreased body weight gains) and 250 mg/kg bw/day (highest dose tested), respectively. Teratogenicity was not observed. Ten to thirteen female rats were administered resorcinol by gavage at doses of 0, 125, 250 or 500 mg/kg bw/day during days 6 – 15 of gestation. No significant differences were observed in fetal parameters (anomalies, and weights) or on resorptions. Teratogenicity was not observed. The maternal and developmental NOAEL was 500 mg/kg bw day (highest dose tested).

Based on the above studies, resorcinol was not a developmental toxicant and did not cause reproductive effects in the rat when administered by gavage or in drinking water.

Some early laboratory animal studies via dermal and oral routes along with human case reports (at high dermal exposures to damaged skin) have suggested that resorcinol may have an effect on the mammalian thyroid. However, no thyroid effects were seen in numerous other studies, including occupational investigations of exposed worker populations. A well-conducted study (OECD TG 416 with detailed evaluation of thyroid endpoints) found no significant effects on the thyroid of rats given up to 233 mg/kg bw/day (males) or 304 mg/kg bw/day (females) in the drinking water through two generations.

Environment

Resorcinol is not expected to disassociate at environmentally relevant pHs (pKa = 9.81.) Resorcinol is not expected to undergo direct photolysis. The overall OH rate constant for resorcinol is 200 E-12 cm^3/molecule-sec with an estimated half-life of 0.053 days (38.16 minutes) with a hydroxyl radical concentration of 1.5 $\times 10^6$ OH- radicals/cm^3. Based on its chemical structure resorcinol has no functional groups susceptible to hydrolysis under environmentally relevant pH and temperature conditions. Therefore, hydrolysis is not expected to occur. Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 1000 kg/h for each medium, shows the following percent distribution: Air = 0.002%; Soil = 63.8%; Water = 36.1%; Sediment = 0.07%. Resorcinol was biodegradable under aerobic and anaerobic conditions. Several aerobic biodegradation studies are available following inherent and ready biodegradation protocols. In a MITI test following OECD Test guideline 301C, resorcinol was determined to be readily biodegradable with elimination rates being 66.7% after 14 days. Following OECD Test guideline 302B, 97% degradation was observed after 4 days. Under anaerobic conditions, resorcinol was considered to have 95% utilization after 110 days acclimation.

The bioaccumulation potential is estimated to be low based on the log Kow of 0.8, which is supported by a BCF of 3.16 estimated with BCFWIN.

Using EPISUITE, volatilization from a model river and lake are anticipated to be 709.3 and 7738 years, respectively.

The 96-hour LC_{50}s of resorcinol in fathead minnows (*Pimephales promelas*) ranged from 26.8 mg/L (mean measured) to 100 mg/L (nominal) under flow through conditions and from 40 – 60 mg/L under static conditions. In a chronic fish study following OECD early life stage guideline the 7 day EC_{50} (weight) in Zebra fish (*Danio rerio)* was =54.8 mg/L (nominal) and the LC_{50} (embryolethality) was

=262 mg/L (nominal). Under static conditions the 48 hour EC_{50} for the water flea (*Daphnia magna*) was 1.28 mg/L (nominal). Analytical monitoring was not conducted in the study so the measured EC50 may be lower than the nominal EC50. Additional studies are available: however they were typically shorter or longer in duration than current guidelines. In an OECD TG 201 study in *Pseudokirchneriella subcapitata*, the 72 hr $E_bC_{50\ (for\ biomass)}$ was > 97 mg/L (mean measured, highest dose tested) and the NOEC for biomass was = 47 mg/L(mean measured). The corresponding mean measured 72 hr E_rC_{50} values and NOEC for growth rate were > 97 mg/L and = 97 mg/L, respectively. In a chronic fish study following OECD early life stage guideline in *Salmo gairdneri*, the 60 day LOEC (weight) = 32 mg/L and the EC_{50} for lethality and malformations was =260 mg/L while the LC_{50} (total embryotoxicity) was =320 mg/L. In an OECD *Daphnia magna* reproduction test (TG 211) no effects were observed up to the highest concentration tested. Limited data were available in micro-organisms; the 96 hr IC_{50} of 1600 mg/L (methane-producing micro-organisms) and a 24 hr EC_{50} of 7.8 mg/L (*Nitrosomonas*) was reported. In *Eisenia foetida* (earthworms), resorcinol showed no effect on growth rate or body weight; the LC_{100} was = 40000 mg/kg soil dw and the LOEC was = 10000 mg/kg soil dw.

Exposure

Total global production of resorcinol was 48 thousand tonnes (106 million pounds) in 2004. In the Sponsor Country, production volume in 2004 was 24.7 thousand tonnes. Japan is the largest producer of resorcinol globally while the United States is the largest consumer.

Resorcinol is produced commercially worldwide in a few specialized plants. All of these plants use benzene (CAS No. 71-43-2) as the main feedstock and two production routes are used commercially on a large scale. Resorcinol is produced either via sulfonation of benzene under conditions promoting di-substitution in meta position followed by fusion with anhydrous caustic ("classical" route via 1,3-benzenedisulfonic acid) or via hydroperoxidation of 1,3-diisopropylbenzene (CAS No. 99-62-7).

The purity of the material is dependent on the manufacturing method. Technical grade resorcinol is available with a minimum purity of 99.3% (which accounts for over 98% of the total global production) and contains one or more of the following impurities depending upon method of manufacture: <0.2%, catechol, phenol, o-cresol, m-/p-cresol, and 3-mercaptophenol, hydroquinone, acetone and acetylphenol (maximum 0.1% each unless otherwise stated).

In production, this material is handled in closed systems. In order to minimize exposure(s) and gain efficiencies, necessary engineering controls and measures are in place during production and processing. Once produced, resorcinol is transferred into bags (e.g 25 kg) or flexible containers (e.g. 500 kg). When appropriate, personal protective equipment is worn during various procedures at the manufacturing facilities.

The ACGIH and MAK recommended time weighted average (TWA) value for resorcinol is 10 ppm (45 mg/m^3). NIOSH also recommends a short term exposure limit (STEL) of 20 ppm (90 mg/m^3).

Resorcinol is used as a key intermediate in the manufacture of other chemicals. In the United States and Western Europe, resorcinol is used primarily in the production of specialty adhesives and/or as an adhesion promoter for tires and wood products. In Japan, resorcinol's use in hair dyes is addressed by the Standards of Approval for the Manufacture and/or Import of Hair Dyes (Notification no. 533 of the Pharmaceuticals Affairs Bureau) which allows for a maximum concentration of 0.1% in use. In the United States (US), resorcinol's use in cosmetics and other medicinal products is restricted to a maximum concentration of 2% as set forth by the Cosmetics Ingredient Review and US Food and Drug Administration. In the European Union (EU), resorcinol's use in hair dyes is controlled under the Cosmetics Directive 76/768/EEC which allows for a maximum concentration of 5%. In oxidative hair dyes, resorcinol is regulated to a maximum of 5% (in the EU) or below (in US and Japan) but in practice many manufacturers limit the level of free resorcinol in oxidative hair dyes to 1.25%. Resorcinol is limited to 0.5% in shampoos and hair lotions. It is used in pharmaceutical preparations for the topical treatment of skin conditions such as acne, seborrheic dermatitis, eczema, psoriasis, corns and warts. Resorcinol in anti-acne preparations is usually used up to a maximum of 2%. In extreme cases, up to 50% resorcinol is reported in the literature as being used by medical professionals with the intended purpose to wound and disrupt the epidermis. Application times are documented as ranging from 30 seconds to 10 minutes. The prescribing professional must determine

the significance of the benefits when using resorcinol in this manner as it is not consistent with the existing regulations within Japan, the EU and the US.

Resorcinol may be released indirectly during use and disposal of resorcinol containing consumer and professional products. The concentration of resorcinol in food and drinking water is not known.

RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health

The chemical is currently a low priority for further work. The chemical possesses properties indicating a hazard for human health (sensitization). Based on data presented by the Sponsor country, adequate risk management measures are being applied. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment

The chemical is a low priority for further work. The chemical possess properties indicating a hazard for the environment (acute toxicity between 1 and 100 mg/L; no effects were observed up to the highest concentration tested in the 21 day chronic aquatic invertebrate study.) The chemical is readily biodegradable and has limited potential for bioaccumulation.