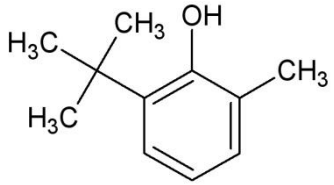
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2219-82-1
Chemical Name	2-Methyl-6-*tert*-butylphenol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical and Chemical Properties

2-Methyl-6-*tert*-butylphenol is a yellow liquid or solid with a melting point of 24-31 °C and a boiling point of 230 °C. Density is 0.924 g/cm^3 at 80 °C and vapour pressure is 3.96 Pa at 25 °C (estimated). The calculated octanol-water partition coefficient (log K_{ow}) is 3.97 and the estimated water solubility is 101.3 mg/L at 25 °C.

Human Health

No specific studies were available on the absorption, distribution, metabolism, or excretion of 2-methyl-6-*tert*-butylphenol. In a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test, oral repeated doses of 2-methyl-6-*tert*-butylphenol caused anemia due to decreased erythrocyte count and hemoglobin concentration. Also, the test substance had effects on hepatic function and increased extramedullary hematopoiesis and hemosiderin deposition in spleen of rats. These results suggested the possibility of absorption of 2-methyl-6-*tert*-butylphenol and distribution in spleen, liver and stomach.

In the acute toxic class method study, LD_{50} cut-off value was considered to be 500 mg/kg bw for female rats [OECD TG 423]. All animals at 2,000 (1st step) mg/kg bw died. At 300 (2nd and 3rd steps) mg/kg bw no death was observed and body weight was normally increased in all animals. Inanimation, prone position, loss of locomotor activity and moribund state were observed after the administration of the test substance at 2,000 mg/kg bw.

The acute dermal LD_{50} value was greater than 2,000 mg/kg bw for male and female rats [OECD TG 402]. Exfoliation was temporarily observed for 5 males and 1 female. No mortality, gross pathology and body weight change were observed.

2-Methyl-6-*tert*-butylphenol was considered to cause skin corrosion in 1 male rabbit [OECD TG 404]. No irritation or corrosion response was observed following 3 minutes and 1 hour exposures. But skin corrosion with skin necrosis, discoloration, erythema (score 3) and edema (score 4) were observed after the 4-hour exposure.

2-Methyl-6-*tert*-butylphenol was tested for eye irritation in three male rabbits according to OECD TG 405. In the initial and confirmatory tests, congestion of the iris (score 1), redness of the conjunctivae (score 1-2), chemosis of the conjunctivae (score 1-2) and discharge (score 3) were temporarily observed. Also, signs of pain, distress, excessive blinking and excessive tearing were observed after the application of the test substance. The maximum mean total score (MMTS) was 17.0. Based on the results, 2-methyl-6-*tert*-butylphenol was considered to cause eye irritation in rabbits under the conditions of this study

In a repeated dose oral toxicity study in rats following OECD TG 422, 2-methyl-6-*tert*-butylphenol was administered via gavage to 12 animals/sex/dose at 0, 8, 40 and 200 mg/kg bw/day. Male rats were treated from 14 days before mating to the day before necropsy (42 days), and female rats were treated from 14 days before mating to day 4 of lactation (42-50 days). As a recovery group, 5/12 males at 0 and 200 mg/kg bw/day were observed for 14 days after the administration period. Additional 5 females at 0 and 200 mg/kg bw/day were treated for 42 days without mating and observed for 14 days as a satellite group. No death was observed in

either sex. Observed clinical signs were prone position, a decrease in locomotor activity, abnormal gait, and irregular respiration in one female of the 200 mg/kg group before mating. Body weight was decreased in females of the 200 mg/kg bw/day group throughout the gestation and lactation periods and in males of the 200 mg/kg bw/day group after day 22. During the recovery period, body weight was also decreased in males of the 200 mg/kg bw/day group. Although body weight gain was suppressed in males on day 22 and females on day 0 of gestation, the body weight gain was comparable to or higher than the control group afterward. Anemic changes were noted in both sexes of the 200 mg/kg bw/day group and increased spleen weight was observed in females of the 200 mg/kg bw/day group. In the spleen, an increase in extramedullary hematopoiesis was noted. After the recovery period, the following changes were noted in the 200 mg/kg bw/day group: anemic findings, increased spleen weight in males, an increase in extramedullary hematopoiesis in one male, an increase in hemosiderin deposition in both sexes. In blood chemistry, high γ-glutamyltransferase and an increasing tendency in aspartate aminotransferase, alanine aminotransferase, and triglyceride were noted in males of the 200 mg/kg bw/day group. Total cholesterol was increased in both sexes of the 200 mg/kg bw/day group. In the liver, the organ weight was increased in both sexes of the 40 and 200 mg/kg bw/day groups and centrolobular hypertrophy of the hepatocytes was seen in both sexes of the 200 mg/kg bw/day group. Other changes in liver disappeared after the recovery period except that an increased liver weight remained in females of the 200 mg/kg bw/day group. Furthermore, treatment-related hyperplasia of squamous limiting ridge in the forestomach was noted in males of the 200 mg/kg bw/day group. Moreover, eosinophil cell infiltration of the glandular stomach and an increase in globule leukocyte were noted in one male of the 200 mg/kg bw/day group. These changes recovered or tended to recover by the end of the recovery period. There were no changes related to the test substance in behavior test, functional test, motor activity, food consumption, urinalysis of males, or necropsy findings. Based on the effects on the anemic changes and liver function noted in both sexes of the 200 mg/kg bw/day group, the NOAEL for repeated dose oral toxicity was considered to be 40 mg/kg bw/day.

In an Ames test with *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 and *Escherichia coli* WP2*uvr*A [OECD TG 471], 2-methyl-6-*tert*-butylphenol did not induce gene mutation in bacteria *in vitro* both with and without metabolic activation. In an *in vitro* chromosomal aberration test [OECD TG 473] using Chinese hamster lung cells, 2-methyl-6-*tert*-butylphenol did not show the structural or numerical chromosome aberrations regardless of application of metabolic activation. Based on these results, 2-methyl-6-*tert*-butylphenol is considered to be non genotoxic *in vitro*.

No reliable studies were available for the carcinogenicity of 2-methyl-6-*tert*-butylphenol.

2-methyl-6-*tert*-butylphenol has been investigated in a combined repeated dose toxicity study with the reproduction/developmental toxicity screening test in rats [OECD TG 422]. 2-Methyl-6-*tert*-butylphenol was administered by oral gavage to 12 animals/sex/dose at 0, 8, 40 and 200 mg/kg bw/day. See the repeated dose section for the dosing regime. During the observation period, gestation length was prolonged at 200 mg/kg bw/day. No abnormality was found in the reproductive organs of either sex. There were no changes in the number of corpora lutea or implantations, implantation index, gestation index, or delivery index, which was considered to have no effect on the implantation or maintenance of the pregnancy. No abnormal findings ascribable to the test substance were found in estrous cycle, mating index, fertility index, sex ratio, external features, or necropsy of the offspring. No effects on body weight of pups were evident in any dose group. The number of live offspring at birth and on day 4, live birth index, and viability index on day 4 were low at 200 mg/kg bw/day. Therefore, the NOAEL for reproduction and developmental toxicity was 40 mg/kg bw/day, respectively.

2-Methyl-6-*tert*-butylphenol possesses properties indicating a hazard for human health (skin corrosion, eye irritation, repeated dose toxicity and reproduction/developmental toxicity via gavage). Adequate screening-level data are available to characterize the human health hazard for the purposes of the Cooperative Chemicals Assessment Programme.

Environment

2-Methyl-6-*tert*-butylphenol does not possess a molecular structure that contains functional groups subject to hydrolysis under neutral ambient conditions. In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is predicted to occur with a half-life of 0.2 day by AOPWIN ver. 1.92. A test for ready biodegradability was conducted with 2-methyl-6-*tert*-butylphenol with activated sludge for 28 days [OECD TG 301C]. The concentration of the test substance was 100 mg/L and the concentration of the activated sludge was 30 mg/L as suspended solid matter. The test results showed 9% degradation by BOD. The DOC and test substance loss was 81% and 98%, respectively. The relevance of the decrease in DOC is unknown. QSAR

estimates support the test result of not ready biodegradability (BIOWIN 4.10). Therefore, 2-methyl-6-*tert*-butylphenol was considered to be not readily biodegradable.

A level III fugacity model calculation with equal and continuous distributions to air, water and soil compartments suggests that 2-methyl-6-*tert*-butylphenol is mainly distributed to the soil (80.1%) and water (17.5%) compartments with a minor distribution to the sediments compartment (2.13%) and a negligible amount in the air compartment. If released only to the soil compartment, 2-methyl-6-*tert*-butylphenol stays in the soil compartment (99.7%) with negligible amounts in other compartments. A Henry's law constant of 0.162 Pa-m^3/mole (6.34×10^{-5} atm-m^3/mole) at 25°C suggests that volatility of 2-methyl-6-*tert*-butylphenol from the water phase is not expected to be high. A log K_{oc} of 3.33 was estimated based on the MCI method, indicating a moderate potential for accumulation in soil.

In 28 days exposure to *Cyprinus carpio*, bioconcentration factor (BCF) of 34~114 and 28~59 were obtained at 0.2 mg/L and 0.02 mg/L, respectively. Using an octanol-water partition coefficient (log K_{ow}) of 3.97, a bio-concentration factor (BCF) of 115.9 was estimated based on regression method with BCFBAF ver. 3.01. Therefore, this chemical has a low potential of bioaccumulation.

The following acute toxicity test results have been determined for aquatic species:

Fish [*Oryzias latipes*, OECD TG 203]	96 h LC_{50}=5.1 mg/L (measured; semi-static)
[*Oryzias latipes*, Japan CSCL]	96 h LC_{50}=4.32 mg/L (measured; semi-static)
Invertebrate [*Daphnia magna*, OECD TG 202]	48 h EC_{50}=3.08 mg/L (measured; static)
[*Daphnia magna*, Japan CSCL]	48 h EC_{50}=5.25 mg/L (measured; static)

Algae [*Pseudokirchneriella subcapitata*, Japan CSCL] 72 h ErC_{50}=6.31 mg/L (growth rate, measured; static)

2-Methyl-6-*tert*-butylphenol possesses properties indicating a hazard for the environment (acute aquatic toxicity between 1 and 10 mg/L for fish, invertebrate and algae). The chemical has a low bioaccumulation potential and is not readily biodegradable. Adequate screening-level data are available to characterize the environmental hazard for the purpose of the Cooperative Chemicals Assessment Programme.

Exposure

In the Republic of Korea (sponsor country), the production, use and import volumes of 2-methyl-6-*tert*-butylphenol were 2,889, 3,099 and 200 tonnes in 2006, respectively. And the production and use volumes were 168 and 8 tonnes in 2010, respectively.

2-Methyl-6-*tert*-butylphenol is used as an antioxidant, stabilizing agent, or in synthetic materials. In the sponsor country, 2-methyl-6-*tert*-butylphenol is mainly used as an antioxidant. The industrial manufacture process of antioxidants is as follows: the raw material, o-cresol, is alkylated with isobutylene. The product is purified by hot filtration.

In the sponsor country, 2-methyl-6-*tert*-butylphenol is manufactured and used in closed systems. Workplaces are under control in accordance with the MSDS. Occupational exposure is managed by local ventilation system and wastewater in the process is well controlled by physical and chemical treatment. Since worker exposure may include inhalation exposure, workers are equipped with personal protective equipment such as gas masks, safety cap, rubber gloves, rubber boots and goggles. Occupational exposure is considered to be properly controlled in the sponsor country.

2-methyl-6-*tert*-butylphenol is used only industrially in the Republic of Korea. Therefore, consumer exposure is not expected in the sponsor country.