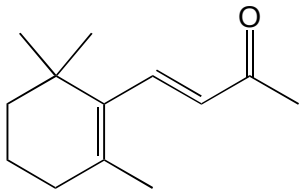
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	79-77-6
Chemical Name	β-Ionone [(E)-4-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-buten-2-one]
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

From animal experiments it can be concluded that β-ionone is absorbed after oral exposure. Metabolism takes place mainly in the liver. Metabolites, which were identified in the urine of exposed rabbits, are 3-oxo-β-ionone, 3-oxo-β-ionol, dihydro-3-oxo-β-ionol and 3-hydroxy-β-ionol. β-Ionone was found to be an inducer of CYP 1A and 2B isozymes in the liver of rodents.

β-Ionone has only low acute toxicity after oral ingestion. A gavage study conducted with a mixture of 60 % α-Ionone and 40 % β-ionone revealed a LD_{50} of 4590 mg/kg bw. Clinical signs of toxicity were depression and tremors.

In studies conducted according to OECD test guidelines and under GLP conditions, β-ionone was not irritating to the skin of rabbits after semiocclusive application for 4 hours and only slightly irritating to the eyes. After a 24-hours exposure under occlusive conditions, a slight irritation of the skin was observed in rabbits. A limited human patch test did not reveal a potential for skin irritation when a not further specified mixture of α- and β-ionone was applied undiluted to the skin of volunteers.

A limited Guinea pig maximization test found no evidence that β-ionone is a dermal sensitizer. According to secondary sources, ionone (a not further specified mixture of α- and β-ionone) was negative in an open epicutaneous test with Guinea pigs as well as in a human maximization test with a product containing 97.5 % α-ionone and 2.5 % β-ionone.

The administration of β-ionone over a period of 90 days according to OECD TG 408 at dietary concentrations of 100, 1000 and 10 000 ppm (7 and 8 mg/kg bw/day, 72 and 83 mg/kg bw/day or 720 and 801 mg/kg bw/day for males and females) to rats led to signs of general systemic toxicity at the high and mid dose. Target organs were liver, kidneys and thyroid glands. The liver findings in both sexes and the increased kidney weights in high dose females were indicative of adaptive and most likely reversible processes with the aim to increase the metabolizing and/or excretory capacity of these organs. The findings in males with respect to kidneys as well as kidney relevant parameters should be seen in the light of high amounts of alpha2u-globulin in these animals. The occurrence of alpha2u-globulin was confirmed by immunohistochemical examination. The accumulation of this protein appears to be a unique feature of male rats and is not known to occur in other species, including man. No signs of neurotoxicity were observed during functional observational battery as well as measurement of motor activity performed towards the end of the administration period.

Thus, the no-observed-effect-level (NOEL) under the conditions of the present study was 100 ppm for both sexes (about 7 and 8 mg/kg bw/day for males and females) based on adaptive liver effects in both sexes and minor urine findings in males at 1000 ppm which correspond to a dosage of 72 and 83 mg/kg bw/day for males and females (no-observed-adverse-effect-level, NOAEL). The lowest-observed-adverse-effect-level (LOAEL) was found at 10 000 ppm (720 and 801 mg/kg bw/day for males and females) due to liver, kidney and thyroid findings in both sexes.

β-Ionone gave no indication of a mutagenic effect in bacteria or a clastogenic potential in an *in vivo* mouse micronucleus test. Therefore, there is no indication of a genotoxic potential *in vivo*.

No studies that would be considered adequate for the evaluation of carcinogenic potential were available. A short-term screening experiment investigating a tumor-promoting potential on mouse skin did not indicate such an effect at a low test concentration.

In a well-conducted 90 days study in rats according to OECD TG 408 with administration of the test substance in the diet, β-ionone did not have the potential to damage the reproductive organs at least up to the highest tested concentration of 10,000 ppm (720 and 801 mg/kg bw/day for males and females).

Based on the results of a GLP and guideline conforming developmental toxicity study (OECD TG 414) with gavage application of β-ionone, the no observed adverse effect level (NOAEL) for maternal toxicity was 100 mg/kg bw/day. The NOAEL for prenatal developmental toxicity could be fixed at the highest tested dose (400 mg/kg bw/day). The test substance had no influence on gestational parameters and induced no adverse signs of developmental toxicity and in particular no indications of teratogenic effects up to and including the highest dose level were observed.

Environment

The colorless to yellowish liquid β-ionone has a water solubility of about 0.169 g/l and a vapor pressure of about 0.009 hPa at 25 °C. The measured log K_{OW} of 4.0 at 25 °C, the calculated log K_{OC} of 2.80 - 3.34 and the calculated BCF of 501 indicate a potential for bio- and geoaccumulation. According to distribution modeling using Mackay Level I, water (34 %), soil (27 %), sediment (27 %) and air (12 %) are the main targets for the compound. β-Ionone is with > 70 % (within 28 days, 10-day-window criteria fulfilled) readily biodegradable according to OECD criteria. In the atmosphere, it will be rapidly photodegraded by reactions with OH radicals (calculated $t_{1/2}$: 1.6 hours) and ozone (calculated $t_{1/2}$: 18 minutes).

Results on acute aquatic toxicity are available for fish (*Pimephales promelas*; LC_{50} (96 hours): 5.1 mg/l), invertebrates (*Daphnia magna*; EC_{50} (48 hours): 3.7 mg/l) and algae (*Scenedesmus subspicatus*; $E\mu C_{50}$ (72 hours): 22.2 mg/l; EbC_{50} (72 hours): 21.2 mg/l). Based on these acute toxicity studies, β-ionone is considered as toxic to aquatic organisms. No results on prolonged or chronic toxicity to aquatic organisms are available. According to the EU risk assessment procedure, a $PNEC_{aqua}$ of 3.7 µg/l was obtained by applying an assessment factor of 1000 on the lowest $L(E)C_{50}$ value, the result of the test with *Daphnia magna*.

Exposure

In the year 2003 the world production of industrial β-ionone was between 4000 and 8000 tonnes/a and in Europe between 1000 and 5000 tonnes/a. In the Sponsor country the production volume of the sole producer is between 1000 and 3000 tonnes/a. The production in USA and Asia was < 1000 tonnes/a and < 2000 tonnes/a, respectively.

In the Sponsor country about 70 % of the manufactured industrial β-ionone is used as intermediate internally for complete consumption in chemical processes for the synthesis of fine chemicals (e.g. vitamins, aroma chemicals). About 30 % of β-ionone are distributed to industrial clients which are using the substance as intermediate for chemical syntheses or directly as flavoring compound and/or aroma additive in e.g. food.

Exposure to β-Ionone occurs via food, cosmetics and some house wares like cleaning agents (flavoring compound, aroma additive). In cosmetics usual concentrations are up to 0.3 % and in food maximum amounts added ranging from 0.5 – 10 ppm. β-ionone occurs also naturally in food (some plants e.g. corn) and plant extracts used for example in perfumes. Typical use concentrations in final products are 0.03 % (soap), 0.003 % (detergent), 0.016 % (creams, lotions) and 0.3 % (perfume). β-Ionone is listed in the Danish, Norwegian and Swedish product register and not listed in the Swiss product register. For Denmark and Norway the use in consumer preparations (Denmark: cleaning / washing agent) is stated.

The substance naturally occurs as a biogenic volatile organic compound and shows a ubiquitous occurrence in the air due to emissions from plants or surface waters. For instance, β-Ionone was found in concentrations ranging from 0.002 µg/l up to 1.2 µg/l in waters of lakes and rivers mainly due to biotransformation processes in phytoplankton. Further, it was measured in red wine with 0.72 µg/l and was described as a volatile compound in beef flavor. It was also identified in several fruits as well as in drinking water- and in wastewater samples. The odor threshold is indicated with 0.007 ppb or 56 ng/m³ based on vapor.

In the Sponsor country (Germany) worker protection is adequate and includes the use of appropriate technical equipment during substance handling and the use of protective equipment, etc.

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

Human Health: The only hazards identified are slight irritation to the eyes and changes in the liver, kidneys and thyroid after repeated oral exposure, which were either of minor severity or were considered to be a species-specific effect in male rats. Given the main use as a chemical intermediate and the low content of the substance in consumer products in the Sponsor country, the chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: β-Ionone possesses properties indicating a hazard for the environment. Based on the data presented by the Sponsor country (relating to production by one producer which accounts for approx. 10 – 40 % of global production and relating to the use in several OECD countries), exposure to the environment from human production and use of β-ionone is anticipated to be low, and therefore this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.