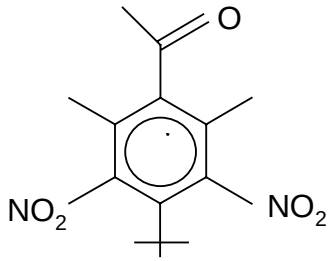
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	81-14-1
Chemical Name	3,5-dinitro-2,6-dimethyl-4-tert-butyl acetophenone (Musk ketone)
Structural Formula	

RECOMMENDATIONS

The chemical is a candidate for further work for the environment and human health.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

The oral LD_{50} for rats and the dermal LD_{50} for rabbits are both greater than 2000 mg/kg bw. Data for acute inhalation toxicity are not available.

Musk ketone is not considered to be irritating for skin and eyes and is not a skin sensitiser. For respiratory tract irritation no data are available.

In a well performed dermal 90-day study with rats effects at the highest dose of 240 mg musk ketone kg/bw included a decreased body weight gain without a concomitant decrease in food consumption, decreases in red blood cell parameters and an increase in absolute and relative liver weight without a histopathological correlation. The decrease in body weight gain was also seen in females at the lower dose of 75 mg/kg bw. In the experiment no neuropathological effects, no effects on the reproductive organs, and no skin effects were seen. Therefore 24 mg/kg bw can be established as the NOAEL in this study. When administered as part of a fragrance mixture, inhalatory exposure to musk ketone up to a maximum tested dose of 170.5 $\mu g/m^3$ for 4 h per day, 5 days per week for 13 weeks did not result in any toxicity.

Musk ketone was negative in several *in vitro* tests (bacterial gene mutation tests, SOS chromosome aberration tests, a mammalian gene mutation test, a micronucleus test in mammalian cells *in vitro*, a SCEs in mammalian cells and an UDS test). A test for chromosome aberration in CHO cells provided an equivocal result, but as an *in vivo* mouse micronucleus test was negative, it can be concluded that musk ketone is a non-genotoxic substance.

With respect to carcinogenicity no data are available on musk ketone. Neither from the available repeated dose toxicity studies, nor from the genotoxicity data an indication is obtained that musk ketone might be a carcinogenic substance. In view of the similarities in structure with musk xylene the carcinogenic study with musk xylene can be considered for the evaluation of musk ketone as well. The conclusion for musk xylene is as follows:

Musk xylene is considered to be a carcinogen in mice acting by a non-genotoxic mode of action. The only tumours reported were liver carcinomas (malignant) in B6C3F1 mice, a mouse strain prone to develop this kind of tumours, and benign malformations in the Harderian gland. The latter type of tissue does not occur in humans and therefore these benign tumours are difficult to interpret with respect to their relevance to humans. It is concluded that there is limited evidence for carcinogenicity of musk xylene in animals as was also stated by IARC.

With respect to fertility no generation study was available for either route. In the 90-day dermal toxicity study with rats, musk ketone caused no effects on the reproductive organs.

In an oral peri/postnatal toxicity study (exposure of the F_1-generation to musk ketone was only *in utero* during the peri-natal phase or through any transfer in the milk of the lactating dams) slight toxicity (decreased body weight gain and food consumption) was seen at the highest dose level of 25 mg/kg bw in the dams. Pup toxicity at this dose included a lower weight and a later day of attainment for surface and air righting and fluxual maturation. The F_1 males in the mid dose of 7.5 mg/kg also had a marginal, but statistically significant lower body weight gain. Dosing up to 25 mg/kg bw did not result in behavioural changes or in reduced reproduction capacity. The lowest dose tested, 2.5 mg/kg bw/d, can be considered as the NOEL in this study. However, the effect at the next higher dose is very small, limited to males and is of uncertain biological significance. In a well performed oral developmental study with rats, maternal toxicity occurred in a dose related way at 45 and 150 mg/kg bw/day. This toxicity included reduced body weight gain, reduced food consumption and increased post implantation loss.

Developmental toxicity, including reduced fetal body weight, was only seen at 150 mg/kg bw/day. Therefore, the NOAEL for maternal toxicity can be established at 15 mg/kg bw, the lowest dose tested, and the NOAEL for developmental toxicity can be established at 45 mg/kg bw. No developmental toxicity studies are available for the dermal and inhalatory route.

The available data obtained from the peri/post natal study indicate that musk ketone can be secreted into the milk into sufficient quantities to elicit toxic responses in the offspring of the test animals.

In a 90-day dermal toxicity study with rats no indications for a neurotoxic potential was found for musk ketone.

Environment

EUSES (Simple Treat) estimates the following default distribution for musk ketone in an STP: air: 0%, water 68% and sludge: 32%. Based on the structure musk ketone is not expected to hydrolyse. Photodegradation has been demonstrated, but is expected to be minimal in the aquatic environment. Musk ketone is not readily biodegradable. The measured BCF in rainbow trout is 1380 L/kg, which is in agreement with the calculated BCF based on log Kow.

The lowest (L)EC50 values for musk ketone were 0.24 and > 0.46 mg/l for algae (growth rate)and Daphnia, respectively. NOEC values were derived for algae, daphnia (21-d) and fish (21-d): 0.088, 0.17 and 0.033 mg/l, respectively. For musk ketone two long-term terrestrial toxicity tests are available: for a shredder (4 weeks, springtail) and a detritivorous species (8 weeks, earthworm). The NOECs are 100 and 32 mg/kg soil, respectively. Musk ketone does not bind to the estrogen receptor in fish (*Oncorhynchus mykiss*) and clawed frog (*Xenopodus laevis*) *in vitro*. For the metabolites 2-amino musk ketone binding in both species was observed. The relevance of these *in vitro* tests for the environment is still unclear.

Exposure

Musk ketone is a solid powder, with a melting point of 135-137 ^{o}C. The Log Kow is 4.3. Using a vapour pressure of 0.00004 Pa at 20 ^{o}C and a water solubility of 0.46 mg/l a Henry's law constant of 0.026 Pa.m^3/mol is calculated.

The use volume of musk ketone in 1998 in Europe is approximately 40 tonnes, including export to non-EU countries. The use volumes are decreasing. There is no production of musk ketone in the EU. Industry sources estimate that 20-30% of their products is exported outside the EU as finished fragrance compounds or in consumer products. Musk ketone can enter the aqueous and terrestrial environment via formulation sites and private use. The calculated exposure concentration in air from formulation sites are minimal.

There is a potential for occupational and consumer exposure through inhalation and skin contact although exposures via inhalation are expected to be low due to the low vapour pressure. Consumer exposure to musk ketone will occur principally through its use in cosmetics. Indirect exposure via the environment is also possible.

NATURE OF FURTHER WORK RECOMMENDED

Sufficient information exists to address hazard classification for all SIDS endpoints and for other non-SIDS endpoints.

The chemical is a candidate for further work for the environment because:

- it is not readily biodegradable
- it has bioaccumulating potential (BCF > 1000 but < 2000) and
- its long-term toxicity (NOEC < 1 mg/l)

The chemical is a candidate for further work for human health because:

- exposure via breast milk can occur
- the effects on pups in the peri/post natal study cannot be disregarded.

In view of these hazards, national or regional exposure information gathering and risk assessment may be considered.

The EU risk assessment is close to completion.