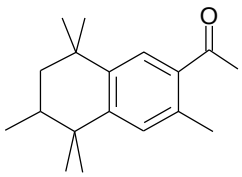
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	1506-02-1 or 21145-77-7
Chemical Name	1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one (AHTN)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical properties

AHTN is a white crystalline solid with a melting point of > 54 °C and a boiling point of 326 °C. The vapour pressure is 0.0682 Pa at 25 °C. AHTN has a measured water solubility of 1.22 mg/l at 25 °C and a pH of 7. The log Kow as determined by the slow stirring method was 5.4.

Human Health

The available data show oral absorption but do not allow establishment of an exact absorption percentage. Based on urine, cage washing and tissue levels from a 2-week oral study in rats, oral absorption of at least 50% can be concluded. The metabolic profile in urine, faeces and liver samples revealed the formation of numerous and complex metabolites. Only metabolised AHTN was detected in the urine and liver; extensive levels were seen in the faeces. There are no data available on the toxicokinetics of AHTN after inhalation exposure. Besides other available studies the main study, an in vitro dermal absorption study using human epidermal membranes (with a 1% solution in ethanol), indicated that 4.1% of the applied dose is absorbed over 24-hr. Intravenous administration of AHTN to rats and the pig resulted in rapid distribution. Excretion in the rat is primarily via the faeces as was seen in the dermal study but in the pig the principle route of excretion is via urine, similar to what was seen in the human study. Only metabolised AHTN was present in the urinary radioactivity in these studies. AHTN is found in human milk in several studies, ranging from undetectable levels up till 565 µg AHTN/kg milk fat.

The oral LD_{50} for rats ranged from 825 – 1377 mg/kg bw and the dermal LD_{50} for female rats is 7940 mg/kg bw. Data for acute inhalation toxicity are not available. Upon acute oral exposure, clinical signs included lethargy, piloerection and signs of emaciation.

AHTN is not corrosive and not irritating to the skin, as determined from irritation studies in animals and humans. In relevant studies, AHTN can be considered to be a minimal eye irritant in rabbits. No data on respiratory tract irritation are available.

AHTN is not a skin sensitiser as determined from animal and human studies. Because AHTN absorbs in the UV region, studies to detect a possible photoirritation or photosensitisation hazard have been conducted, in both animals and humans. In the photoirritation studies in animals,

minimal dermal irritation was observed after irradiation with UV light. Photoirritating effects were not found in human studies. Also, the 3T3 NRU Phototoxicity Test in vitro was negative. In animal studies investigating photosensitising effects, mostly positive results were reported, whereas only negative results were reported in human studies on photosensitisation. The positive results may be due to sensitising effects from photodegradation products arising from the interaction of AHTN and UV light, evidenced from a study in guinea pigs where two of the four photodegradation products of AHTN reacted positive. Therefore AHTN can be a photosensitiser in animals but this effect was not seen in humans.

In a 28-day oral gavage study according to OECD Guideline 407 with 5 animals/sex/dose, rats were exposed to 0, 1, 3 or 10 mg/kg bw/day AHTN in Oleum maydis germinis (total dose volume
10 ml/kg bw). No effects were seen at doses up to and including 10 mg/kg bw/day (the highest dose tested). In a 90-day oral study according to OECD Guideline 408 with 15 animals/sex/dose, rats received by dietary admixture nominal doses of 0, 1.5, 5, 15 and 50 mg AHTN/kg bw/day. Clear mild haematological effects were seen at the highest dose administered, 50 mg/kg bw/day. These effects may be associated with observations of dark discolouration of the liver and mesenteric lymph nodes seen in most high dose animals but not in animals at lower doses. Observations in animals maintained on a treatment-free regime for 28 days following the 90-day treatment period indicate that all effects are reversible. Although the differences from controls were small and generally within historical ranges seen for rats in this laboratory, the overall pattern is such that it cannot be excluded that these effects are of adverse nature. At the lower doses, some statistically significant differences from controls in blood biochemistry and haematology were found, but these differences were small and within the values for historical controls. Some of these, however, showed a dose-response relationship at 15 and 50 mg/kg bw/day. The green colouration of the lachrymal gland was clearly dose-related but not associated with any histopathology at any dose in any animal. The most likely explanation for this observation is accumulation of a pigment resulting from reaction of a photo-oxidation product of AHTN with proteins, and this finding, albeit undesirable, is not considered an adverse effect. Therefore the systemic NOAEL is 5 mg/kg bw/day, based on the marginal effects observed at 15 mg/kg bw/day.

Repeated dose toxicity studies after inhalation exposures are not available for AHTN.

From none of the three conducted sub-chronic dermal studies of AHTN in rats, primarily designed to screen for possible neurotoxicity as observed for a structural closely related substance, it is possible to establish a NOAEL, due to several shortcomings.

In a sub-acute study with i.p. administration, AHTN did not show peroxisome proliferating and cytochrome P450 inducing properties.

AHTN has been tested in a wide array of in *vitro* tests and in an *in vivo* mouse micronucleus test. *In vitro*, AHTN was negative in gene mutation tests with bacteria with and without metabolic activation, in an SOS chromotest with bacteria with and without metabolic activation, in SCE and micronucleus tests with human cells with and without metabolic activation and in an UDS test with primary rat hepatocytes. Equivocal results were obtained for AHTN in one *in vitro* chromosome aberration test in CHO cells. However, AHTN did not induce chromosome aberrations in the *in vivo* micronucleus test. Hence, it can be concluded that AHTN is a non-genotoxic substance.

There are no carcinogenicity test data available. AHTN is demonstrated to be not genotoxic. There are no indications from repeated dose toxicity studies, which could be used to judge the carcinogenic potential. It has been shown that AHTN has no liver tumour initiating and promoting activity in rats exposed to human-relevant doses.

No standard multi-generation studies are available. However, no effect on reproductive organs was found in the 13-week oral (dietary) repeated dose toxicity study with rats, after administration of doses of up to 50 mg/kg bw/day to female and male rats. In a peri/postnatal study no effect on reproduction performance was found.

In an oral peri/postnatal toxicity study, rats were exposed once daily by gavage to doses of 0, 2, 6, or 20 mg/kg bw/day from day 14 of pregnancy through to weaning on day 21 post partum. Exposure of the F1-generation to AHTN was only in utero during the perinatal phase or through transfer in the milk of the lactating dams. No toxicity was seen at dose levels of 2, 6 or 20 mg/kg bw/day in the dams or their F1 and F2 offspring. A NOAEL of 20 mg/kg bw/day can be established, the highest dose tested.

In an oral developmental study, AHTN in corn oil was administered by gavage to groups of 25 female rats on days 7 through 17 of presumed gestation at dosages of 0, 5, 15 and 50 mg/kg bw/day. Maternal toxicity occurred at 50 mg/kg bw/day, the highest dose tested. Therefore, the NOAEL for maternal toxicity can be established at 15 mg/kg bw/day. Developmental toxicity was not seen up to the highest dose administered (50 mg/kg bw/day), the developmental NOAEL is therefore 50 mg/kg bw/day (the highest dose tested).

AHTN has a very weak estrogenic potency *in vitro* but no such effect is seen *in vivo* in an uterotrophic assay in non-ovariectomized mice but otherwise similar to OECD TG 440 at dosages of 2 and 6.5 mg/kg bw/day (10 and 50 ppm in the diet of mice for 2 weeks).

AHTN does not present a concern for reproductive/developmental toxicity based on the information available.

AHTN does not present a hazard for human health due to its low hazard profile. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

AHTN is considered hydrolytically stable, because the molecule does not contain any functional groups that would react with water. Under atmospheric conditions direct photolysis by sunlight and gas phase reaction with OH radicals are considered to be the major degradation routes for AHTN. Based on the estimated rate constant of 1.7×10^{-11} cm^3 $molecule^{-1}$ sec^{-1} and assuming a daylight period of 12h and OH radical concentration of 1.5×10^6 OH-radicals/cm^{-3}, the calculated atmospheric half-life is 7.3 hours. The half-life for degradation by UV radiation in lake water was determined at 4 hours in a laboratory set-up comparable to mid-summer clear sky sunlight conditions at 50°N. In standard tests for ready or inherent biodegradation AHTN did not biodegrade. In a primary biodegradation process AHTN is rapidly transformed to a series of more polar metabolites. In a river water die-away study with 10 mg activated sludge to simulate surface water conditions at the point of discharge, the disappearance of ^{14}C-labeled parent material and the formation of metabolites was determined. The overall half-life was 9 days and the biological degradation (primary) was over 40% in 28 days. In a sludge die-away study a half-life of 12 to 24 hours was observed, with 59% present as metabolite after 28 days. In a Continuous Activated Sludge test with realistic sewage treatment plant operation conditions, half of the total removal of AHTN from the water phase (87.5%) was caused by biotransformation (42.5%) and half was caused by sorption (44.3%), whereas volatilization played a minor role (3.3%). Residues in soil, expressed as the sum of AHTN and HHCB (CAS nr. 1222-05-5), in fields with regular sludge application were well below 1% of the estimated applied amount within a few years after the last sludge application.

A level III fugacity model with equal and continuous distribution to air, water and soil compartment suggest that AHTN will distribute in air 0.1%, water, 2.2%, soil, 33.3% and sediment 64.4%. The measured Henry's Law Constant is 37.1 Pa m^3/mol at 25 °C. The calculated log Koc, based on log Kow is 4.47 and is

within the range of the measured log Koc values (3.0 to 4.8 in various matrices). The measured bioconcentration factor of AHTN determined according to OECD TG 305E is 597 in bluegill sunfish and 600 in zebrafish. The half-life for elimination was less than 2 days.

Acute aquatic toxicity data are available:

Taxon	**Test species**	**Endpoint**	**Result mg/L**	**Guideline**	**M/N****
Fish	*Lepomis macrochirus* Bluegill sunfish	96h-LC_{50} (survival)	1.49	OECD TG 204	M
Invert	*Daphnia magna*	72h-EC_{50}* (mobility)	> 0.80	OECD TG 202-part 2	M
Alga	*Pseudokirchneriella subcapitata*	72h-EC_{50} (growth rate Biomass)	> 0.835 0.63	OECD TG 201	M
Invert	*Acartia tonsa* [marine]	48h-LC_{50} (survival)	0.71	draft ISO/DIS 14669	N
Invert	*Nitocra spinipes* [marine]	48h-LC_{50} (survival)	0.61	draft ISO/DIS 14669	N

* Derived from OECD 202-part 2 test (see below).
**N: nominal; M: measured.

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

Taxon	**Test species**	**Endpoint**	**Result mg/L**	**Guideline**	**M/N***
Alga	*Pseudokirchneriella subcapitata*	72h-NOEC (growth rate)	0.405	OECD TG 201	M
Invert	*Daphnia magna*	21d-NOEC (reproduction)	0.196	OECD TG 202-part 2	M
Invert	*Acartia tonsa* [marine]	6d-EC10 (larval development ratio)	0.028	OECD draft TG (life cycle test) (2004)	M
Fish	*Lepomis macrochirus* Bluegill sunfish	21d-NOEC (growth)	0.089	OECD TG 204	M
Fish	*Brachydanio rerio* Zebrafish	34d-NOEC (growth, development)	0.035	OECD TG 210	M
Fish	*Pimephales promelas* Fathead minnow	36d-NOEC (growth, development)	0.035	OECD TG 210	M

*N: nominal; M: measured.

Toxicity tests were carried out with three species of sediment organisms according or similar to OECD TG 218. The 28-day NOEC for the midge larvae *Chironomus riparius* was 101 mg/kg dwt (development), for the amphipoda *Hyalella azteca* 18.2 mg/kg dwt (growth) and for the aquatic oligochaete worm *Lumbriculus variegates* 7.1 mg/kg dwt (growth) at an organic carbon content of 2%. Toxicity tests were also carried out with soil organisms. The 8-week NOEC (reproduction) for earthworm *Eisenia foetida* according to OECD TG 207 was 105 mg/kg and the 4-week NOEC (reproduction) for the springtail *Folsomia candida* 45 mg/kg according to ISO/CD 11267.

AHTN may present a hazard for the environment (acute aquatic toxicity values below < 1 mg/L and not readily biodegradable). Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

AHTN is produced on one site in Europe, with a production volume in the year 2000 between 1000 and 5000 ton/y. Circa 62% of the production volume is exported outside Europe. Use volumes are according to RIFM (Research Institute of Fragrance Materials) and IFRA (International Fragrance Association) based on regional surveys carried out between 1993 and 2006. For the countries belonging to EU-15 plus the two associated countries Norway and Switzerland, the use volumes declined from 885 ton per year in 1992, 358 ton per year in 2000 (used for the quantification of the industrial releases in the SIAR) to 247 ton per year in 2004. Environmental release of AHTN may occur during production, during compounding, during formulation and during/after use by consumers. It is assumed that the total use volume is discharged to the sewer.

AHTN is used as an ingredient in fragrance oils (fragrance oils is also referred to in literature as fragrance compounds, fragrances, fragrance composition, perfume oil or perfume compositions). AHTN is the second largest volume product of the fragrance materials known collectively as polycyclic musks. Fragrance oils are complex mixtures, prepared by blending (compounding) many fragrance ingredients in varying concentrations. Most of these ingredients are liquids, in which AHTN is dissolved. Applications of the fragrance oils are mainly in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products and air fresheners. Blending of the fragrance oil with other ingredients to make the final consumer product is often referred to as a formulation.

Occupational exposure is possible during production, during compounding, during formulation and during cleaning by professional cleaners. As AHTN has a very low vapour pressure, exposure to vapour is considered negligible. Dermal and inhalation occupational exposure to pure AHTN and dermal exposure to mixtures containing AHTN are relevant. Compounding fragrance oils and formulating consumer products involve a high level of automation, intensive ventilation and a high working accuracy required to prevent any cross contamination. Professional cleaners may be exposed to AHTN while using cleaning products and dermal exposure may occur each time hands are submersed in the diluted cleaning solution.

Consumer exposure may occur following dermal and inhalation exposure of which the dermal exposure is the most relevant.