Adopted as Rule: September 30, 2013

Toxicological Summary for 6-Acetyl-1,1,2,4,4,7 hexamethyltetraline: CAS: 21145-77-7 or 1506-02-1

Synonyms: AHTN; Tonalide; Musk tetralin; Polycyclic musks; 7-Acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphthalene;Acetyl-hexamethyl-tetrahydronaphthalene; 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphthyl)ethan-1-one

Acute Non-Cancer Health Risk Limit ($nHRL_{acute}$) = Not Derived (Insufficient Data)

While developmental studies in animals are available, the quantity and quality of the information is not sufficient to derive an acute guidance value. Based on the available information, the short-term HRL for AHTN is protective of developmental effects.

Short-term Non-Cancer Health Risk Limit ($nHRL_{short\text{-}term}$) = 100 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Short-term intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.070 mg/kg/d) x (0.5) x (1000 µg/mg)}}{\text{(0.289 L/kg-d)}}$$

= 121 rounded to **100 µg/L**

Reference Dose / Concentration:	0.070 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	32 mg/kg-d (NOAEL); 14-day dietary range-finder study (Api et al. 2004)
Human Equivalent Dose Adjustment:	7 mg/kg-day [32 mg/kg-day x 0.22] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty (lack of multi-generational reproductive study)
Critical effect(s):	Increased severity of hepatocyte fine vacuolation
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Subchronic Non-Cancer Health Risk Limit ($nHRL_{subchronic}$) = 30 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Subchronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.011 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.077 L/kg-d)}}$$

= 28 rounded to **30 µg/L**

Reference Dose / Concentration:	0.011 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	5 mg/kg-d (NOAEL), Subchronic dietary study (Api et al. 2004)
Human Equivalent Dose Adjustment:	1.1 mg/kg-day [5 mg/kg-day x 0.22] (MDH, 2011)
Total uncertainty factor:	100
UF allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics); 10 for intraspecies variability; 3 for database uncertainty (lack of multi-generational reproductive study).
Critical effect(s):	Effects on various biochemical liver parameters including increased A/G ratio, reductions in plasma glucose, cholesterol, and plasma triglyceride
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Chronic Non-Cancer Health Risk Limit ($nHRL_{chronic}$) = 20 µg/L

$$= \frac{\text{(Reference Dose, mg/kg/d) x (Relative Source Contribution) x (Conversion Factor)}}{\text{(Chronic intake rate, L/kg/d)}}$$

$$= \frac{\text{(0.0037 mg/kg/d) x (0.2) x (1000 µg/mg)}}{\text{(0.043 L/kg-d)}}$$

= 17 rounded to **20 µg/L**

Reference Dose / Concentration:	0.0037 mg/kg-d (rats)
Source of toxicity value:	MDH 2012
Point of Departure:	5 mg/kg-d (NOAEL), Subchronic dietary study (Api et al. 2004)
Human Equivalent Dose Adjustment:	1.1 mg/kg-day [5 mg/kg-day x 0.22] (MDH, 2011)
Total uncertainty factor:	300
UF allocation:	3 for interspecies extrapolation (to address potential differences in toxicodynamics); 10 for intraspecies variability; 3 for subchronic to chronic extrapolation (comparison of 7 and 13-week assessments suggested minimal changes; however, limited duration specific information precludes complete removal of uncertainty factor); 3 for database uncertainty (lack of multi-generational reproductive study).
Critical effect(s):	Effects on various biochemical liver parameters including increased A/G ratio, reductions in plasma glucose, cholesterol, and plasma triglyceride
Co-critical effect(s):	None
Additivity endpoint(s):	Hepatic (liver) system

Cancer Health Risk Limit (cHRL) = Not Applicable

Cancer classification: No cancer classification is available for AHTN

Slope factor: Not applicable
Source of slope factor: Not applicable
Tumor site(s): Not applicable

Volatile: Yes (moderate)

Summary of changes since 1993/1994 HRL promulgation:
In 2011 Short-term, Subchronic and Chronic Health-Based Values (HBVs) of 200, 40, and 20 µg/L were derived. MDH reevaluated the HBVs in 2012 to incorporate HED methodology. Of the resulting Short-term, Subchronic and Chronic HBVs (100, 30 and 20 µg/L), the Short-term and Subchronic values were lower (2-fold and 1.3-fold) than the values derived in 2011 and the Chronic value remained the same. These HBVs were adopted into rule as HRLs in 2013.

Summary of toxicity testing for health effects identified in the Health Standards Statute:

	Endocrine	Immunotoxicity	Development	Reproductive	Neurotoxicity
Tested?	Yes	Yes	Yes	Yes	Secondary observation[5]
Effects?	No[1]	Yes[2]	Yes[3]	No[4]	Yes[5]

Note: Even if testing for a specific health effect was not conducted for this chemical, information about that effect might be available from studies conducted for other purposes. Most chemicals have been subject to multiple studies in which researchers identify a dose where no effects were observed, and the lowest dose that caused one or more effects. A toxicity value based on the effect observed at the lowest dose across all available studies is considered protective of all other effects that occur at higher doses.

Comments on extent of testing or effects:
[1.] AHTN has been reported to have very weak estrogenic and anti-estrogenic potency *in vitro* and an antagonist effect on estradiol in zebrafish. AHTN also had marginal repressing *in vitro* effects on androgen and progesterone receptors. However, no estrogenic effects were seen in an *in vivo* mouse uterotrophic assay; therefore, AHTN is not currently considered to be a mammalian endocrine disruptor *in vivo*. However, the mouse uterotrophic assay may not have been sufficient to detect subtle estrogenic effects because the mice were not fully immature at the end of the 2-week exposure period. Possible dose-related effects on uterine distension and pro-estrous cyclicity were reported in rats exposed to AHTN in the diet for 13 weeks; however, these effects are not well-characterized and the RfDs for liver effects are considered protective of potential endocrine effects because uterine and pro-estrous effects were noted at doses approximately 15, 100 and 300-fold higher than the short-term, subchronic, and chronic RfDs, respectively.

[2.] AHTN has not been tested directly for systemic immunotoxicity. AHTN was non-sensitizing via dermal contact in animals or humans. AHTN is considered to be a potential photosensitizer after irradiation with u.v. light. No secondary effects on immune system organs were observed in a 13-week dietary study.

[3.] AHTN is not generally considered a developmental toxicant even when tested at doses that were maternally toxic. However, at high doses in a range-finder study (over 300 times greater than the short-term RfD and about 6,000 times greater than the chronic RfD), some fetuses had whole-body edema, although statistical significance was not presented. Therefore, the short-term, subchronic and chronic values are protective of potential developmental effects.

[4.] No effects on reproductive organs were found in a 13-week oral study examining male and female reproductive and accessory organs. AHTN was not a reproductive toxicant in a peri/postnatal study that evaluated neurobehavioral effects; however, dosing was limited to the period during pregnancy after

organogenesis (missing the most sensitive exposure period for most developmental effects) through lactation and the study was not a standard multi-generational reproductive study where exposures would continue for a prolonged period of time before pregnancy and post-lactation.

[5.]Neurotoxicity was evaluated by the dermal route of exposure. AHTN was determined to be non-neurotoxic in dermal subchronic studies. In an animal study with oral exposure during pregnancy (after organogenesis) through lactation, the offspring did not exhibit neuro-behavioral effects. The study exposure period, however, was limited and did not cover a broader period before mating and during the lifetime of the offspring that is typical of standard multigenerational reproductive studies. AHTN given by gavage during gestation caused maternal nervous system toxicity in rats as exhibited by decreased motor activity and excessive salivation at a dose approximately 300 times greater than the short-term RfD and about 6,000 times greater than the chronic RfD.

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