1-(5,6,7,8-TETRAHYDRO-3,5,5,6,8,8-HEXAMETHYL-2-NAPHTHYL)ETHAN-1-ONE

(AHTN)

CAS No: 1506-02-1 or 21145-77-7

EINECS No: 216-133-4 or 244-240-6

SUMMARY RISK ASSESSMENT REPORT

Final report, 2008

The Netherlands

FINAL APPROVED VERSION

Rapporteur for the risk assessment of AHTN is the Ministry of Housing, Spatial Planning and the Environment (VROM) in consultation with the Ministry of Social Affairs and Employment (SZW) and the Ministry of Public Health, Welfare and Sport (VWS). Responsible for the risk evaluation and subsequently for the contents of this report is the rapporteur.

The scientific work on this report has been prepared by the Netherlands Organization for Applied Scientific Research (TNO) and the National Institute of Public Health and the Environment (RIVM), by order of the rapporteur.

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PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance AHTN that has been prepared by the Netherlands in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

CONTENTS

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 1506-02-1 or 21145-77-7

(The presence of two different CAS numbers for AHTN was caused by an error in the molecular structure for AHTN by one company and a correct and therefore different molecular structure by a second company. Afterwards the molecular structure was corrected. The presence of two CAS numbers from two companies resulted in two EINECS No.)

EINECS Number: 216-204-6 or 244-240-6

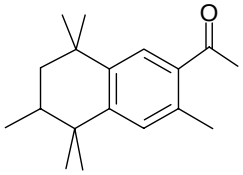
IUPAC Name: 6-Acetyl-1,1,2,4,4,7-hexamethyltetraline

Synonyms: 1-(5,6,7,8-Tetrahydro-3,5,5,6,8,8-hexamethyl-2-napthyl)ethan-1-one
2'–Acetonaphtone,5',6',7',8'-tetrahydro-3',5',5',6',8',8'-hexamethyl
6-Acetyl-1,1,2,4,4,7-hexamethyl-1,2,3,4-tetrahydronaphtalene
6-Acetyl-1,1,2,4,4,7-hexamethyltetraline
7-Aceto-1,1,3,4,4,6-hexamethyltetraline
7-Aceto-1,2,3,4-tetrahydro-1,1,3,4,4,6-hexamethylnaphtalene
7-Acetyl-1,1,3,4,4,6-hexamethyl-1,2,3,4-tetrahydronaphtalene
AHMT
AHTN
Ethanone,1-(5,6,7,8-tetrahydro-3,5,5,6,8,8-hexamethyl-2-naphtalenyl)-
Fixolide
Tentarome
Tetralide
Tonalid

Molecular weight: 258.41

Molecular formula: $C_{18}H_{26}O$

Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Purity: ≥ 98% w/w

Isomers: The molecular structure of AHTN has one stereogenic centre so there are two enantiomers. The enatiomer ratio in technical AHTN is 1:1.

Impurities: 6-Acetyl-3-isopropyl-1,1,3,5-tetramethylindane, ca. 0.35% w/w
1,1,2,3,3,6-Hexamethylindan-5-yl methyl ketone, ca. 0.18% w/w (CAS-No 15323-35-0)
7-Acetyl-1,1,3,4,4,6-hexamethyltetraline, ca. 0.08% w/w

Additives: none

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Result	Comment
Physical state	Solid, granules	
Melting point	> 54 °C	
Boiling point	326 °C at 1 atm	
Relative density	Bulk density: 600 kg/m^3 Density: 600 kg/ m^3 < D_4^{20} < 960 kg/m^3	92/69/EEC A.3
Vapour pressure	0.0682 Pa at 25 °C	gas saturation method, OECD TG 104, ^{14}C-labelled material
Water solubility	1.25 mg/l at 25 °C # (1.31 mg/l at pH 5; 1.22 mg/l at pH 7 and 9) 0.4 mg/l 0.91 (± 0.04) mg/l	flask method, OECD TG 105, ^{14}C-labelled material calculation (SRC) column elution method
Partition coefficient n-octanol/water (log value)	5.7 6.35 6.25 5.4 #	reversed-phase HPLC, OECD TG 117 calculation calculation slow stirring method
Granulometry Particle size distribution	10% < 140.6 µm 25% < 270.6 µm 50% < 479.1 µm 75% < 686.7 µm 90% < 810.0 µm	Laser diffraction analysis
Flash point		not applicable, melting point > 54 °C
Autoflammability temperature	no spontaneous ignition	Dir. 92/69/EEC A.16
Flammability	non flammable	Dir. 84/449/EEC A.10
Explosive properties	not explosive	Expert judgement
Oxidizing properties	not oxidizing	Bretherick's Handbook of Reactive Chemical Hazards, Ed. 1995 by P.G. Urben
Henry's Law Constant	37.1 Pa.m^3/mol determined at 25°C #	equilibrium partitioning in closed system and SPME

: value selected for environmental risk assessment

1.4 CLASSIFICATION

Classification and Labelling: Symbols: Xn, N

R-phrases: R22, R50/53

S-phrases: S(2-)46, 60, 61

2 GENERAL INFORMATION ON EXPOSURE

Production

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.

Uses

The crystallised product is used as an ingredient in fragrance oils; sometimes in literature also referred to 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 many fragrance ingredients in varying concentrations. Most of these ingredients are liquids, in which AHTN is dissolved. Applications of the fragrance oils are in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products and in air fresheners.

In Europe there are approximately 26 larger and medium sized compounding sites that receive AHTN. A fraction of the production is directly used into bulk formulation of consumer products, such as the preparation of detergents by the larger producers. The fraction directly used is estimated at 20%.

For the exposure calculations for the life-cycle part 'private use' the volume for 2000 of 358 ton will be used. The use of detergents per inhabitant is lower in some northern European countries than in southern Europe, with a maximum difference between Italy and Finland of a factor of 3.3. However, the highest per capita use (Italy, 12.6 kg per year) is above the EU average (10.1 kg) only by a factor of 1.25. The use of cosmetics (expressed in monetary units) is lowest in some southern countries. Yet the highest consumption in the EU, in France (€ 174), is above the EU average (€ 147) by a factor of 1.18 only.

Trends

There are two factors that may cause an uneven distribution of the use volume of AHTN *per capita* in Europe. A ‘cultural’ factor of different use volumes of detergents may cause a higher use of detergents per capita by factor of 1.25 in southern EU countries (Italy, Spain, Portugal, France, 166 million inhabitants), whereas an average use volume is found in Belgium/Luxembourg, Greece, UK and Ireland, with 84.6 million inhabitants. In the Northern countries (Germany, Austria, Netherlands, Denmark, Sweden and Finland) with 125.5 million inhabitants, the detergent use is below average by a factor of 0.7. The second factor is the market development factor, where since 1995 polycyclic musks are gradually being replaced by other fragrance ingredients. As a maximum this would result in a higher use in the southern countries by factor of 1.5 as compared to the average *per capita* use of AHTN. As both factors are independent, the combination gives a factor of $1.25 \cdot 1.5 = 1.88$ above the average use in a ‘worst case scenario' for the year 2000. For 2000 an evenly distributed use would mean 358 ton/370 million inhabitants (0.97 g *per capita* per year) and to cover the uneven use in a realistic worst case scenario this would be $1.88 \cdot 0.97 = 1.81$ g *per capita* per year (Southern EU). In the northern countries the minimum use volume would be the maximum/3.3 = 1.81/3.3 = 0.55 g *per capita* per year, whereas there the highest level would theoretically be 1.0 · EU-average = 0.97 g *per capita* per year. The regional use is 10% of

the total use. This is used by 20 million inhabitants in the region, resulting in a *per capita* use of 1.79 g per year.

Legislative controls

No legislative controls are in place at the time of reporting.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Environmental releases

An overview of all relevant data used for calculation of emissions for production, compounding and formulation is given in Table 3.1. The data are based on visits to the production and larger compounding sites. Information for the smaller compounders and for formulation was obtained through analysis of sales data.

Table 3.1. Summary of relevant data for production, compounding and formulation, based on the year 2000

Compounding site	Volume of AHTN, kg/year	# of working days per year	Emission factor after treatment,%	Conc. in influent to STP, µg/l	PECsurface water, µg/l
Production	1000-5000 ton	259	-	0.111	0.021
Comp. 1	4,500	240	0.02	0.2	0.008
Comp. 2	6,000	250	0.05	0.3	0.059
Comp. 3	31,140	250	0.016 – 0.048	1.8	0.002
Comp. 4	40,600	250	0.06	36.1 (WWTP)	0.009
Comp. 5	10,400	250	0.008 – 0.002	0.04	0.010
Comp. 6	94,000	250	0.00	0	
Comp. 7 – Generic scenario for a large/medium site	16,000	250	0.06 *	19.2 #	0.42
Comp. 8 – Generic scenario for a small site	358	125	0.2 **	2.9 #	0.069
Large formulator	19,000	345	0.017	4.7	0.109
Generic small formulator	286	250	0.2 #	6	0.131

* Higherst release rate after treatment from the sites visited (1-6)
** Highest empirically derived overall scrap factor for large/medium compounding site 5
# TGD realistic worst case calculations

The total volume of AHTN in end product formulation in Europe for 2000 is assumed to be 358 tonnes. The number of sites in the EU-15+2 is estimated on the basis of the number of members of the branch organisations involved in the production of end products (soaps/detergents and cosmetics industry in the EU-15+2), which is likely to be over 2000. As a conservative estimate, 1000 sites in the EU-15+2 are assumed.

No specific information was available for deliveries by compounders to formulators. The use volume by these formulators is 358 ton minus the 20% sold directly to the formulators, thus 286 ton/year. The use of AHTN on an average formulator site is 286 ton / 1000 = 0.286 ton per year. For the assessment of a 'reasonable worst case, this use volume is multiplied by a factor of 5, thus 1430 kg/year (or 0.4% of total use). With the emission factor to waste water

of 0.2% and 250 working days per year for a small formulator, the loss to the STP is 11.4 g/day.

Cosmetics will be emitted to waste water to a lesser extent than detergents. As a first approach for the estimation of the PECs, it is assumed that the total volume of AHTN used in compounding fragrances in Europe for 2000, i.e. 358 tonnes is released to waste water going to a STP. Since the high and low estimates of the scenarios for private use differ only by a factor of 3, the estimations are first carried out according to the default TGD regional (10%) scenario resulting in 4.9 mg. cap^{-1}. day^{-1}. The use of these consumer products is mostly associated with water that will be discharged to the sewer system. Therefore the disposal phase is already included in the use phase. The disposal of residues in empty containers is expected to be a minor volume; moreover it is expected to be disposed of as solid waste in a controlled way.

In summary, AHTN may be released during the production phase, during compounding and formulation and during/after use by consumers. For the risk assessment, as a conservative approach, it is assumed that the total volume used in fragrance compounding is discharged to the sewer.

Environmental fate

Under atmospheric conditions the half-life is estimated at 7.3 hours. The half-life in a laboratory set-up with lakewater was 4h (summer conditions, 50 ºN).

In a primary degradation process, AHTN is rapidly transformed to polar metabolites. These substances still contain the same amount of organic carbon and only a small fraction of the theoretical oxygen demand has been incorporated. Thus this metabolism is in agreement with the observed low degree of mineralisation. In batch experiments with activated sludge spiked with radio-labelled AHTN, the half-life of the parent compound AHTN was less then 1 day and within 20 days AHTN was largely transformed to metabolites. In the river water die-away test the overall half-life was circa 9 days and the biological degradation after 28 days was 42%. In soil studies the residual AHTN present after 9 months ranged from below 42 to 61% of the initial concentrations. Comparison of the results in the available tests with those for HHCB showed that the half-life of AHTN in sludge and in soil was similar to that for HHCB or twice as long as for HHCB. For the environmental risk assessment, AHTN may be considered as inherently biodegradable', not fulfilling criteria'. For surface water, sediment and soil, the biodegradation rate constants are based both on the data for AHTN and on the results for HHCB. As a conservative approach, the rates for AHTN are taken as twice the rates for HHCB: 150 d in surface water (20 ºC) and 365 d in the soil and sediment compartments (12 ºC).

A K_{oc} value for AHTN can be estimated from the K_{ow} value of 5.4 using the QSAR recommended for predominantly hydrophobics: $\log K_{oc} = 0.81 \cdot \log K_{ow} + 0.10$. Using this equation a $\log K_{oc}$ value of 4.47 can be estimated. The theoretical partition coefficients derived from EUSES are compared to experimentally derived data. It is concluded that the empirical values vary considerably but the predictions by EUSES are within that range. Therefore the calculations were carried out with the predictions made by EUSES on the basis of $\log K_{ow}$.

Using a vapour pressure of 0.0682 Pa and a water solubility of 1.25 mg/l a Henry's Law Constant of 14.1 Pa.m3/mol is calculated. The Henry's Law Constant was empirically determined at 37.1 $Pa.m^3/mol$. The latter was used in the PEC calculations.

According to the SimpleTreat model, AHTN entering an STP partitions between the sludge, water and air. The partitioning is predicted on the basis of K_{oc}, water solubility and vapour pressure. Then the fraction in the water phase is degraded according to the rate constant assigned to inherently degradable substances (TGD: 0.1 h^{-1} or 0 h^{-1}). In EUSES the volume of domestic waste water is set at 200 l/d *per capita*, the solids production from the STP is 79 g/d *per capita*, and the concentration of suspended solids in the effluent is 30 mg/l. With log K_{ow} = 5.4 and k_{biodeg} = 0, the fate of AHTN in an STP is predicted by EUSES. The available studies are not conclusive on the quantisation of the biodegradation of AHTN in an STP. Therefore the EUSES model is used for local industrial scenarios (Table 3.2) whereas the estimation of PEClocal for consumer use is based on the concentrations measured in effluent and sludge in recent monitoring programmes.

Table 3.2 Distribution of AHTN in an STP (%) predicted by EUSES and observed in a CAS test

	EUSES predictions % of input to STP	**CAS test, mass balance (Lee et al. 2001) (parent,% of dosed)**
Air	9.2	3.3
Water	20.6	12.5
Sludge	70.2	44.3
Degraded	0 (rate = 0 h^{-1})	42.5 (1st-order rate constant 0.029 – 0.057 h^{-1})

The bioconcentration of AHTN in fish was studied in various experiments. In a GLP-study according to OECD TG 305E, Bluegill sunfish (*Lepomis macrochirus)* were exposed in a flow-through system to radio labelled AHTN. The fish were exposed for 28 days; the elimination period was also 28 days. The concentration of AHTN in the fish reached plateau levels after 3-7 days of exposure. An uptake rate constant (k_1) could not be directly calculated from the increase of concentrations in fish due to rapid attainment of the final plateau level. Elimination followed first order kinetics with a half-life of 0.8 - 2.1 days, allowing calculation of the rate constant for elimination (k_2). Based on concentrations of parent material, the BCF for the whole fish was 597, which is used for the environmental risk assessment.

The bioconcentration of AHTN in two benthic organisms was described. Fourth instar midge larvae (*Chironomus riparius*) and the worm *Lumbriculus variegatus* were exposed in a flow-through system. The organisms were not fed during the 12d-exposure period. *C. riparius* the result was given as log BCF = 1.7 to 2.05; for the worm the result was log BCF = 3.84 which is at the same level as the predicted BCF based on K_{ow} and lipid content.

The bioconcentration in earthworms is assumed to be proportional to the soil pore water concentration, leading to a BCFworm of 3015 $l \cdot kg^{-1}$. Transfer coefficients were determined in lettuce and carrots growing on sludge amended soil samples. It is concluded under normal conditions that transfer of AHTN from the soil to plants is not relevant.

Available studies indicate that the enantiomeric ratio in environmental samples is the same as in technical AHTN, used as reference. Selective transformation of one of the 2 enantiomers was observed in one fish species (an ER between 1.6 and 2.0). In 4 other fish species and in zebramussels minor to no enantioselective transformation was observed. Toxicity and ecotoxicity studies have been carried out with technical AHTN. As the enantiomeric ratios in

the environment are generally the same as in this material, no recalculation or correction is needed for the risk assessment. The values can be directly compared.

Aquatic compartment (incl. sediment)

For consumer use, various scenarios were used, including the TGDregional (10%) based on a use of 4.9 mg. cap^{-1}. day^{-1} and the southern and northern European countries based on concentrations measured in effluents and on sludge. In the latter two scenarios, PECregional was scaled in proportion to these measurements.

The comparison of predicted concentrations and those measured in influents is limited to the more recent data, starting from the year 2000. A large number of observations for AHTN in STP influents is reported from Germany and there are some from other European countries, for example The Netherlands, Switzerland, Austria, Spain and the UK. The predicted influent concentrations in the scenarios for northern and southern European countries were based on the calculations where the release factor was reduced to obtain the observed effluent concentrations. The predictions by the TGD regional (10%) scenario are too high by almost two orders of magnitude.

The estimations from the TGD regional (10%) scenario predicted PECeffluent = 20.2 µg/l. For the Northern EU-15 Scenario the recent data for Germany were used as the start of the calculations for the Northern EU-15 (90^{th}-percentile, 0.54 µg/l), whereas the data for Italy, Spain and Greece were the basis for the calculations of the Southern EU-15 Scenario (overall 90^{th}-percentile, 1.3 µg/l). Recently reported data from Austria and Sweden are in line with the Northern EU-15 Scenario. For the risk characterisation the Southern EU-15 Scenario is used: **PECeffl = 1.3 µg/l (total).**

The concentration in sludge predicted by the TGD regional (10%) scenario = 174 mg/kg dwt. For the Northern EU-15 Scenario the calculations were made using the 90^{th}-percentile of recent data for Germany, 5.9 mg/kg dwt and for the Southern EU-15 Scenario, the overall 90^{th}-percentile of the results in Spain, Italy and Greece was used, 11.0 mg/kg dwt.

The Northern EU-15 Scenario predictions are based on effluent concentrations recently measured in Germany by applying a dilution factor of 10. It is concluded that in general these predictions are at the same level as the most recent values in Germany. As the SEU-15 Scenario is also based on recent effluent concentrations, it is concluded that the SEU-15 Scenario is acceptable except maybe for places with a lower dilution potential than the default 1:10. For the risk assessment the Southern EU-15 Scenario will be used: **$PEClocal_{water}$ = 0.13 µg/l.** The 90^{th}-percentile of the surface water samples in the high effluent input area in Berlin (1996/1997) was 0.91 µg/l.

The predictions based on the current effluent and sediment concentrations predict the sediment concentrations relatively well. Therefore the sediment concentrations predicted based on effluents and sludge concentrations measured in the Southern EU-15 can be used for the risk assessment: **$PEClocal_{sediment}$ = 0.086 mg/kg wwt ~ 0.395 mg/kg dwt.**

Terrestrial compartment

The predicted concentrations in agricultural soil after 10 years of sludge application are 0.014 and 0.027 mg/kg wwt (0.03 mg/kg dw) for the Northern and the Southern EU-15 Scenarios respectively. Measured concentrations in soil are scarce and hardly suitable for comparison. The observations from the field in the US where sludge is regularly applied twice per year show concentrations < 0.05 mg AHTN/kg dw after one half year. The study in Baden-

Württemberg, Germany suggests that after applications similar to the scenario described in the TGD, concentrations were below 0.001 mg AHTN+HHCB/kg dw. The concentrations found in the floodplains of the river Elbe were below 0.01-0.02 mg/kg dw. It is concluded that all reported concentrations are below PEClocal. The detection levels limit the comparison with PECregional. For the risk assessment the SEU-15 scenario will be used: **$PEClocal_{soil}$ = 0.027 mg/kg wwt.**

Atmosphere

The concentrations observed in ambient air in Norway are below PECregional air. The concentrations over Lake Michigan were below PEClocal level in the TGD scenario and just at PECregional in the TGD scenario (but conditions are not related). From the concentrations measured in rainwater a wet deposition flux may be derived, assuming 700 mm rain/year. 700 mm per year equals 1.92 l of rain per m^2 per day. With the medians of 4.1 and 13 ng/l of rain, the deposition is 0.007 - 0.025 µg/m^2/d. These results are above the total deposition flux estimated for The Netherlands by a factor of 2 to 10. In view of the variability in weather conditions, rainfall, sunshine, the results seems to match relatively well.

Secondary poisoning

Concentrations measured in fish are reported from both very heavily polluted areas and from more remote regions, in Germany, The Netherlands, Italy, Switzerland, Czech Republic, Norway, the North Sea and USA. AHTN was detected in most samples except in fish caught in remote areas, lakes and on sea. The highest concentrations by far were observed in the areas classified as 'high effluent input' areas in Berlin, Germany, in 1996-1997. The levels found in the Czech Republic (1997-2000) are reported based on the fraction of lipids. The data for the species that are shared with the Berlin study indicate that the maximum levels in Czech fish are below those in fish from the high effluent input area in Berlin by a factor of 10. It has been shown that the levels in effluents discharged into the high input areas in Berlin have decreased considerably, as is also reflected in the current sediment concentrations in the Teltow Canal. Thus it may be expected that the levels in fish are also reduced considerably. No recent data are available for comparison with the Northern European Scenario (0.0165 mg/kg wwt). When comparing $PECoral_{fish}$ for the Southern European Scenario (0.04 mg/kg wwt) to the data other than from the high effluent input area in Berlin, this PEC is exceeded also in areas with lower levels of contamination. Apparently the input for the predictions (the current effluent and sludge concentrations in southern Europe) is at a lower level than it was in Germany at the time the fish were sampled. Thus for the risk assessment the Southern EU-15 Scenario cannot be used. The risk assessment will be based on the TGD regional (10%) scenario since it covers all monitoring data except for some historic extremes in the Berlin area: **$PECoral_{fish}$ = 0.628 mg/kg wwt.** The 90^{th}-percentile for all fish in the Berlin area (1996/1997) was 0.57 mg/kg wwt.

Marine compartment

For an assessment of the exposure of the marine environment a local exposure assessment was performed for the generic compounding sites (site 7 and 8), for the generic formulators and for the private use scenarios for northern and southern European countries. For a default assessment industrial trade effluents of sites along the coast are not treated in a municipal biological STP. After discharge of the STP (2000 m^3), the water flow becomes 20,000 m^3 per day. A dilution factor in the marine environment of 100 is assumed, so the water flow for dilution in the marine environment is 200,000 m^3 per day. By default the dilution factor for mixing of river water into the coastal sea is 10, so $PECregional_{seawater} \simeq 0.1 \cdot$

$PECregional_{water}$. $PECregional_{seawater}$ is estimated by EUSES. When the presence of an STP is taken into account in the calculations, PECmarine roughly equals $0.1 \cdot PECfreshwater$. According to a survey among compounders and formulators in the EU, the treatment of waste water in a sewage treatment plant is common practice. As the fraction discharged with the effluent is 0.206 (according to EUSES), the values after treatment are roughly 0.206 of the values predicted for the default scenario.

For releases to municipal waste water of substances used for private or public use (IC5 and IC6), the degree of treatment in a biological STP corresponds to the inland scenario. Therefore the effluent concentration from the STP (southern EU-15) is used as a starting point for the assessment. $PEClocal_{seawater}$ (dissolved) is simply derived from Ceffluent with a dilution factor of 100 and a correction for the sorbed fraction. The concentrations in marine sediment and in the food of predators and top-predators are calculated for all scenarios taken in consideration for the marine risk assessment, see Table 3.3.

Table 3.3. Predicted concentrations in fish, exposure of marine predators

Scenario, mg /d per capita	PECregional seawater, µg/l	PEClocal seawater, µg/l	PEClocal $_{sediment}$ mg/kg wwt	PECoral predator mg/kg	PECoral top-predator, mg/kg
Production, compounding and formulation					
Compounding Site 7 (Large-medium generic)	0.000718	0.184	0.120	0.0554	0.0114
Compounding Site 8 (Small generic)	0.000718	0.0274	0.018	0.0086	0.0021
Formulation Large company	0.000718	0.0437	0.0284	0.0133	0.0030
Formulation generic	0.000718	0.0553	0.036	0.017	0.0037
Private use					
TGD regional (10%)	0.00759	0.201	0.138	0.062	0.0161
southern EU-15	0.000718	0.0131	0.0087	0.0041	0.0012
northern EU-15	0.000156	0.0054	0.004	0.0017	0.00041

3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. sediment)

For the determination of the PNEC various results of prolonged toxicity tests are available for algae, the invertebrates Daphnia and Acartia, and fish that were fully reported and carried out according to GLP requirements. Tests are also available for other species of the class of crustaceans, insects, molluscs, annelids and amphibians, however, the validity of these data cannot be established as critical pieces of information are lacking (information on actual test concentration, dose-response, variability of replicates, control survival, etc.). Based on the results of the prolonged tests, the lowest value is the EC_{10} of 0.028 mg/l for the larval development of the marine crustacean *Acartia tonsa.* Therefore with an assessment factor of 10, **$PNEC_{water}$ is 2.8 µg/l**. For microorganisms no specific toxicity tests have been carried out. In the biodegradation tests, no inhibition was observed, implying that the NOEC is above 30

mg/l. With an assessment factor of 10, the **$PNEC_{STP}$** would be > 3 mg/l. This PNEC is above the water solubility of AHTN of 1.25 mg/l.

PNECsediment is determined from the results of the three tests with the midge larvae, amphipods and worms. These tests were carried out, according to the protocol, in a substrate containing 2% organic carbon. In the TGD, PECsediment is derived for sediment containing 5% organic carbon and thus NOEC needs to be standardised to 5% organic carbon. The lowest NOEC is 17.2 mg/kg for the growth of worm *Lumbriculus variegatus*. Since there are tests with benthic species of three different taxonomic groups an assessment factor of 10 is applied to the lowest of the NOECs, giving **$PNEC_{sediment}$** of **1.72 mg/kg dwt**. Based on the equilibrium partitioning theory, **$PNEC_{sediment,\ EqP}$ = 8.42 mg/kg dwt**. The PNECsediment based on sediment toxicity tests and the one derived by equilibrium partitioning from PNECwater differ by a factor of 5.

Terrestrial compartment

No data are available on the toxicity to plant and specific microorganisms in soil. Two long term toxicity tests are available, allowing an assessment factor of 50 to be applied to the lowest NOEC. However, first this lowest NOEC is normalised to the standard soil of the TGD containing 3.4% of organic material: 45 / 0.1 ·0.034 = 15.3 mg/kg. Therefore **$PNEC_{soil}$ = 0.31 mg/kg dwt or 0.28 mg/kg wwt**. If $PNEC_{soil}$ were derived from $PNEC_{aqua}$ by equilibrium partitioning, $PNEC_{soil,\ equil}$ = 1.84 mg/kg wwt or 2.1 mg/kg dwt.

Atmosphere

No data are available and no $PNEC_{air}$ can be derived.

Secondary poisoning

No specific toxicological data are available on e.g. (fish-eating) birds. The PNEC for secondary poisoning will therefore be based on mammalian toxicity data for AHTN. A NOAEL of 5 mg/kg bw/d is derived from the 90-day oral study with rats. As toxicity is based on the P-generation (rats > 6 weeks) a conversion factor of 20 has to be used resulting in a NOEC of 100 mg/kg food (e.g., in fish). For the derivation of $PNEC_{oral}$, the test duration of 90 days implies an assessment factor of 90, giving $PNEC_{oral}$ = 1.1 mg/kg food. In a 21-day reproduction and development toxicity study, the NOAEL was $\geq$ 20 mg/kg/d (no LOAEL established). With the same conversion as above, the NOEC in food is $\geq$ 400 mg/kg. With an assessment factor of 300 (as for a 28 day test) $PNEC_{oral}$ is >1.3 mg/kg food. In conclusion, **$PNEC_{oral}$ = 1.1 mg/kg food.**

Marine effects assessment

Results are available from long-term tests with species from three trophic levels: algae as the primary producers, *Daphnia* and *Acartia* as primary consumers and fish as secondary consumers. Therefore the Assessment Factor is 100 (instead of 10 used in the freshwater compartment), applied to the lowest EC_{10} of 28 µg/l for the marine copepod *Acartia tonsa*. Therefore the **$PNEC_{marine\ water}$ = 0.28 µg/l**. The PNEC for the marine sediment is derived from three long-term sediment tests with species representing different living and feeding conditions, implying that an assessment factor of 50 is applied to the lowest NOEC of 3.75 mg/kg wwt (OC-normalised). Thus **$PNEC_{marine\ sediment}$ = 0.075 mg/kg wwt or 0.345 mg/kg dwt.**

Other effects

Other effects reported in literature include endocrine interactions evidenced by studies *in vitro* and in transgenic fish, and subcellular interactions with multixenobiotic resistance (mxr) transporters in gill tissue of the marine mussel. In the endocrine interaction studies, a dose-dependent anti-estrogenic activity was observed and in the study in gill tissue a dose-dependent inhibitory effect. The concentration levels at which these effects started to be observed, are at the level of the NOEC used in the effect assessment.

3.3 RISK CHARACTERISATION

Aquatic compartment (incl. sediment)

The PEC/PNEC ratios for the aquatic compartment are presented in Table 3.4. The PNECs used are > 3000 mg/l for the STP and 2.8 µg/l for aquatic organisms. $PNEC_{sediment}$ = 0.375 mg/kg wet weight or 1.72 mg/kg dry weight is derived directly from toxicological data, where the intake of AHTN by ingestion of food is taken into account. Thus the risk characterisation is expressed as $PEC/PNEC_{sediment}$ without an additional factor.

For all compounding and formulation scenarios as well as for the production scenario, PEC/PNEC is below 1. Also for the private use scenario which is based on the Southern EU-15 Scenario, the ratio is below 1. An assessment was also carried out for the sediment in the Teltow Canal in Berlin, which was a cause for concern in earlier risk assessments. For completeness the measurements in Berlin in 1996/1997 where the risk quotient was above 1, are included. The current data for the Teltow Canal show that PEC/PNEC is now below 1.

All PEC/PNEC ratios are below 1, hence a **conclusion (ii)** is drawn for all scenarios.

Terrestrial compartment

The PEC/PNEC ratios for the soil compartment are presented in Table 3.4. The PNECsoil of 0.31 mg/kg dwt or 0.28 mg/kg wwt is used. For the risk assessment of the private use the Southern European Scenario is used. The risk ratios for production, compounding and formulation as well as for private use are all below 1. Therefore **conclusion ii** is justified.

Atmosphere

As no $PNEC_{air}$ could be derived, a risk characterisation for the atmosphere is not possible.

Secondary poisoning

The PNECoral for the assessment of secondary poisoning is 1.1 mg/kg. This PNEC is compared with PEC_{oral} for fish as well as for worms. For fish-eating predators, the PECs for private use based on the TGD regional (10%) scenario was used, whereas the PEC for worm-eaters is based on the SEU-15 scenario. An assessment was also performed for the levels measured in fish in the area of Berlin in 1996/1997. The PEC/PNEC ratios are included in Table 3.4.

All PEC/PNEC ratios are below 1 (**conclusion ii**).

Marine risk assessment

With the approach using additional assessment factors of 10 to derive a marine PNEC and a simple approach of a conservative additional dilution factor of 10 in the marine environment, the risk for the marine environment is screened, see Table 3.5. For the private use scenario the marine PEC/PNEC ratios are similar to those in freshwater. All ratios are below 1.

Table 3.4. PEC/PNEC ratios for water, sediment, soil and secondary poisoning

	RCR_{STP} PNEC > 3000 µg/l	**RCR Surface water PNEC = 2.8 µg/l**	**RCR Sediment PNEC = 0.375 mg/kg wwt PNEC = 1.72 mg/kg dwt**	**RCR Soil PNEC = 0.28 mg/kg wwt PNEC = 0.31 mg/kg dwt**	**RCRpred/fish PNECfish = 1.1 mg/kg wwt**	**RCRpred/worm PNECfish = 1.1 mg/kg wwt**
Production, formulation and compounding						
Production	6.67E-06	0.008	0.04	0.002	0.006	0.001
Compounding Site 1	1.33E-05	0.0003	0.01	0.0003	0.004	0.002
Compounding Site 2	2.00E-05	0.021	0.10	0.004	0.02	0.003
Compounding Site 3	1.30E-04	0.001	0.004	0.03	0.001	0.02
Compounding Site 4 (in house WWTP)	2.60E-03	0.003	0.02	-	0.003	-
Compounding Site 5	3.33E-06	0.004	0.02	0.001	0.005	0.001
Compounding Site 6			0.01	-	-	-
Compounding Site 7 (Large-medium generic)	1.14E-03	0.15	0.73	0.27	0.12	0.18
Compounding Site 8 (Small generic)	2.07E-04	0.02	0.12	0.04	0.02	0.027
Formulation Large company	3.37E-04	0.04	0.19	0.07	0.03	0.043
Formulation Generic scenario	4.00E-04	0.05	0.22	0.08	0.04	0.053
Private use						
Southern EU-15	**4.33E-04**	**0.05**	**0.23**	**0.101**		**0.06**
TGD regional (10%)					**0.57**	
measured max. Berlin, Teltow Canal 2003			0.27			
measured 90th percentile Berlin high effluent input area 1996/1997		0.33	(1.3)			
measured 90th percentile Berlin all fish 1996/1997					0.52	

Table 3.5. PEC/PNEC ratios for the marine environment, without and with treatment of industrial water in a municipal STP

	$RCR_{seawater}$	$RCR_{seawater}$ STP included	$RCR_{marine\ sediment}$	$RCR_{seawater}$ STP included	RCRoral predator	RCRpred/worm
	PNEC = 0.28 µg/l		PNEC = 0.075 mg/kg wwt		PNECfish = 1.1 mg/kg wwt	
Production, formulation and compounding						
Compounding Site 7 (Large-medium generic)	2.56	0.14	1.6	0.33	0.05	0.010
Compounding Site 8 (Small generic)	0.39	0.02	0.24	0.05	0.008	0.002
Formulation Large company	0.61	0.04	0.38	0.08	0.012	0.003
Formulation Generic scenario	0.77	0.04	0.48	0.09	0.015	0.003
Private use						
Southern EU-15		**0.05**		**0.12**	**0.004**	**0.001**

As indicated in the TGD, a generic scenario for an industrial site must use a default assessment, unless site specific information is available, for PEClocal. This default assumes that industrial effluents are not treated in a municipal biological STP but are discharged directly to the marine aquatic environment. A survey confirmed that compounders and formulators using AHTN and HHCB discharge their wastewater into the marine environment only after treatment in a sewage treatment plant. Therefore the default marine scenario used in the calculations is not realistic. When the presence of an STP is taken into account in the calculations, the PECs for marine water and sediment are considerably lower and thus all PEC/PNEC ratios are well below 1.

The risk for food chain effects is expressed as the PEC/PNEC ratio for a predator in the marine food chain and for a marine top-predator. The risk ratios are below 1 for the private use scenario as well as for the default compounding and formulation scenarios the PEC/PNEC ratios are below 1. Therefore no additional calculations were performed with inclusion of the STP. The concentrations measured in marine fish in Norway are also below the PNEC.

Thus all risk ratios are below 1 and a **conclusion ii** is drawn for all marine scenarios.

3.4 PBT ASSESSMENT

For AHTN no data are available from tests that simulate the marine environment in water or sediment. Evidence for rapid degradation is based on die-away studies in river water, resulting in 42% biodegradation of the parent material in 28 days. The overall t½ in river water was 9 days. The rapid primary degradation was characterised by the formation of more polar metabolites which were slowly mineralised. It was also shown that the substance is rapidly metabolised in fish and in midge larvae. Photodegradation in water is observed and is expected to take place in the upper water layer of the marine environment. Under atmospheric conditions the half-life is 7.3 hours. It is concluded that AHTN does not meet the persistence criterion.

Experimental BCF for Bluegill sunfish (*Lepomis macrochirus*) and zebrafish (*Brachydanio rerio*) and BAF-values determined from actual measurements in fish and surface water are ca. 600 for the parent compound. There is an indication that AHTN may accumulate in a lower invertebrate species that is not capable of metabolising the substance. Evidence for the absence of food chain accumulation or biomagnification is shown in predatory organisms in Arctic and marine species. It is concluded that AHTN does not meet the criterion for bioaccumulation.

The lowest (long-term) experimentally derived NOEC is 0.028 mg/l. Based on the results of 6 GLP studies with no ecologically relevant NOECs below 10 µg/l, AHTN does not meet the criterion for environmental toxicity within the scope of the PBT assessment. All toxicological tests performed on mammals only justify the classification harmful when swallowed (R22). AHTN is not listed in the Community Strategy for Endocrine Disrupters (COM(2001)262final) as a substance with suspected or proven ED potential.

It is concluded that AHTN does not meet the criteria for PBT substances.

4 HUMAN HEALTH

4.1 EXPOSURE

4.1.1 Occupational exposure

Occupational exposure assessment has been conducted for production and crystallisation of AHTN, compounding of fragrance oils, formulation of consumer products that contain fragrance oils and for the use of cleaning agents by professional cleaners. As AHTN has a very low vapour pressure, exposure to vapour for all scenarios is considered negligible, unless stated otherwise.

European production of AHTN occurs in one plant in The Netherlands. During site visits and audits, human activities as process operation, crystallisation, analytical measurements, odour quality control and wastewater treatment are recognised. However, based on measured data, crystallisation and incidental maintenance of the cooler are considered relevant for the risk assessment of scenario 1, production and crystallisation of AHTN. Exposure of the skin to liquid or dust is considered negligible during normal process operation or during cleaning operation.

Compounding fragrance oils involve a high level of automation, intensive ventilation and a high working accuracy required to prevent any cross contamination. Although measured data may not represent inhalation exposure to dust and vapour completely, modelled data (EASE) overestimate the exposure during handling of AHTN. Therefore monitoring data is preferred and used for the sub-scenarios: compounding (large & medium size plants) and compounding (small size plants). For dermal exposure an additional sub-scenario is described for compounding while handling a molten form of AHTN. For the sub-scenarios delivery, analysis and odour control, dermal and inhalation exposure are considered negligible due to fully automated sampling, small quantities and short time duration for odour control.

While formulating consumer products containing fragrance oils, dermal exposure may be possible during handling of the drums and during cleaning and maintenance of the equipment. Inhalation exposure is considered negligible due to the strong dilution of the substance and the low vapour pressure.

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.

In Table 4.1 a summary of the occupational exposure assessment of AHTN is presented.

Table 4.1 Summary table of occupational exposure assessment to AHTN

Workers scenario	Inhalation		Dermal			
	Vapour	Dust	Liquid		Dust	
	Concentration		Dose level	% AHTN [b]	Dose level	% AHTN [b]
Scenario 1						
- production (crystallisation)	Negligible	0.1 mg/m^3 4 hr/day	Negligible	Negligible	5.5 mg on 420 cm^2	100%
maintenance of cooler	Negligible	0.6 mg/m^3 2 hr/day (2 times per year)	Negligible	Negligible	no data	no data
Scenario 2						
- delivery	Negligible	Negligible	Negligible	Negligible	Negligible	Negligible
compounding - large & medium size plants	0.013 mg/m^3 [a] 8 hr/day 0.023 mg/m^3 [a] 15 min/day		1 mg/d on 100 cm^2	2%	5.5 mg on 420 cm^2	100%
Compounding - small size plants	0.065 mg/m^3 [a] 8 hr/day 0.1 mg/m^3 15 min/day		1 mg/d on 100 cm^2	2%	5.5 mg on 420 cm^2	100%
- compounding (molten form)			39 mg/day 100 cm^2	100%		
- analysis	Negligible		Negligible	Negligible		
- odour control	Negligible		Negligible	Negligible		
Scenario 3						
- handling	Negligible		0.85 mg/day 420 cm^2	2%		
-cleaning & maintenance	Negligible		0.04 mg/day 1300 cm^2	0.002%		
Scenario 4						
- handling	Negligible		0.16 mg/day 840 cm^2	0.02%		

If no quantification is given in the field, this means that the route of exposure is not applicable. In one plant dermal exposure to liquid may be 39 mg/day on 100 cm^2.

[a] Exposure is assumed to be a combination of vapour and dust.

[b] Because AHTN is a photosensitiser (see chapter 4.2 on effects for details), an effect which is concentration dependent, AHTN exposure is also expressed as '% AHTN'.

4.1.1.1 Consumer exposure

The worst-case estimate of dermal exposure of consumers to AHTN via cosmetics amounts to 0.34 mg/kg bw/day (**Table 4.2**). The inhalatory exposure of consumers to AHTN via air fresheners and cosmetics is lower, in total 0.0046 mg/kg bw/day. These figures are taken forward to the risk characterisation.

Table 4.2 Overview of products and uses that can contain AHTN, adapted from the SCCNFP opinion (2002)

Type of cosmetic product	Application quantity in grams per application	Application frequency per day	Retention factor (%)[5]	AHTN in product (%)	Exposure to AHTN (mg/day)	Exposure to AHTN for 60 kg person (mg/kg/day)
Body lotion[1]	8	0.71	100	0.048	2.7	0.045
Face cream[2]	0.8	2	100	0.036	0.576	0.0096
Eau de toilette[3]	0.75	1	100	0.96	7.2	0.12
Fragrance cream[1]	5	0.29	100	0.48	7.0	0.116
Anti-perspirant /deodorant	0.5	1	100	0.12	0.60	0.010
Shampoo	8	1	1	0.06	0.048	0.0008
Bath products[4]	17	0.29	1	0.24	0.12	0.002
Shower gel[4]	5	1.07	10	0.144	0.77	0.013
Toilet soap	0.8	6	10	0.18	0.86	0.014
Hair spray	5	2	10	0.06	0.6	0.010
				Total	**20.5**	**0.34**

1. Assumes use of conventional body lotion 5 times a week and a fragranced cream twice a week.

2. Including make up and foundation.

3. Including perfume and after shave, but these three products are not used concurrently. The quantity used is inversely proportional to the fragrance concentration so these values include all hydroalcoholic products.

4. Assumes use of bath products twice a week and an average use of shower gel 1.5 times a day, 5 times a week.

5 Proportion of product remaining on the skin.

4.1.2 Man exposed indirectly via the environment

For man exposed via the environment the inhalation and oral route are applicable. The contribution of the inhalation of AHTN via air is negligible compared to other uptake routes, hence only the main oral exposure route via fish and root crops is taken into account.

Using EUSES, the total daily intake via root crops and fish is estimated at 1.8 µg/kg bw/day for the local scenario (large/medium compounding scenario) and 0.012 µg/kg bw/day for the regional scenario as shown in Table 4.3. These values are taken forward to the risk characterization.

Table 4.3 Estimated human daily intake of AHTN via environmental routes

	Estimated human daily intake (mg/kg body weight/day)							
Lifecycle step	**Wet fish**	**Root crops**	**Leaf crops**	**Drinking water**	**Meat**	**Milk**	**Air**	**Total**
Private use SEU scenario	1.30E-4	5. 4E-4	7.63E-6	1.46E-6	1.04E-6	6.11E-7	1.05E-6	6.81E-4
Fraction of total daily dose	0.19	0.79	0.01	0.002	0.0015	0.0009	0.0015	
Large/Medium Compounding	2.74E-4	1.48E-3	1.55E-5	4E-6	2.26E-6	1.33E-6	2.13E-6	1.8E-3
Fraction of total daily dose	0.15	0.83	0.009	0.002	0.001	7E-4	0.001	
Regional, SEU scenario	8.4E-6	3.5E-6	2.6E-7	6.11E-8	3.4E-8	2.0E-8	3.6E-8	1.23E-5
Fraction of total daily dose	0.68	0.28	0.02	0.005	0.003	0.002	0.003	

Note: Daily intake of: drinking water 2 L/day. fish 0.115 kg/day, leaf crops 1.2 kg/day, root crops 0.384 kg/day, meat 0.301 kg/day, dairy products 0.561 kg/day. Inhalation rate: 20 m^3/day. Bioavailability for oral uptake: 0.5. Bioavailability for inhalation: 1. Body weight of human: 70 kg. SEU= Southern Europe.

AHTN has been detected in human milk samples. The source of AHTN in these samples is not entirely clear. Maternal exposure to consumer products, intake via food, water or air and occasionally also occupational exposure may contribute to the AHTN level in milk. However, from the point of view of the child, AHTN in milk is an indirect environmental exposure. Therefore this exposure is dealt with in this section, rather than the sections on consumer or combined exposure.

Several publications on AHTN levels in human milk are available and the results from the study where the highest mean and maximum level were found are forwarded to the risk characterization. In this study, an analysis of the milk from 59 nursing mothers revealed the presence of AHTN with a mean value of 112 µg/kg milk fat. The minimum and maximum values found were undetectable and 565 µg/kg milk fat, respectively. A fat content ranging from 1.5 to 4.2% was also reported. Based on the highest fat content (worst case), human milk contains 4.7 µg/kg whole milk (mean) or 23.7 µg/kg whole milk (maximum).

4.2 EFFECTS

There are no data available on the toxicokinetics of AHTN after inhalation exposure. For inhalation exposure, an assumption of 100% absorption as a worst-case will be used in the risk characterization. The latter assumption would probably overestimate exposure from dust because absorption in the lung is likely to occur only for dissolved AHTN and AHTN is poorly soluble in water (1.25 mg/L).

The available oral absorption data do not allow establishment of an exact absorption percentage. Taking into account physico-chemical properties neither no nor complete oral absorption is likely. Hence, an intermediate default percentage of 50% for oral absorption is taken forward to the risk characterisation. As a support, based on urine, cage washing and tissue levels from a 2-week oral study in rats, absorption of at least 50% can be concluded.

Route-to-route extrapolation introduces an additional uncertainty, not taking into account first pass metabolism.

In an *in vivo* study with rats where AHTN was applied for 6 hr under occlusion in 70% alcohol the amount remaining in the tissues (excluding that at the site of dosing, i.e. 1.5%) at sacrifice (1.7%) and the amount excreted (17.1%), almost all (14.5%) of which was in the faeces, a total absorption of 18.8% can be concluded.

An *in vitro* dermal absorption study with ^{14}C-ring-labelled AHTN using human epidermal membranes indicated that 4.1% of the applied dose is absorbed over 24-hr. This figure is taken forward to the risk characterisation. This is considered to be a worst-case assumption, even for damaged skin, because a study with 3 human volunteers indicates a lower dermal absorption in humans (mean total absorption after 120 hours: 0.9%; maximum: 2%).

Intravenous administration of AHTN to rats and the pig results in rapid distribution. Excretion in the rat is primarily via the faeces as was seen in the dermal study (~ 76% of total excretion compared to ~84% after dermal exposure) but in the pig the principle route of excretion is via urine similar to what was seen in the human study. In neither of these studies, any evidence of accumulation was seen. However, clearance from the fat was slower than from other organs. It is noteworthy that in the intravenous studies, no unmetabolised AHTN is present in the urinary radioactivity. This means that all AHTN present in urine is metabolised (for rat 21.5%, and for pig 86.2%). The faeces (the major excretion route of the rat) were not analysed for metabolites or parent.

AHTN is found in human milk in several studies, ranging from undetectable levels up till 565 µg AHTN /kg milk fat. Values for risk characterization were chosen from the recent study from the Czech Republic with 59 mothers where the highest mean (112 µg AHTN/kg fat) and maximum level (565 µg AHTN/kg milk fat) were found (see section 4.1.2).

In summary, for the purpose of risk characterization, 50% absorption for oral exposure and 100% for inhalation will be used. For dermal absorption of AHTN in rats and humans, values of 20% and 4.1% respectively, are taken forward to the risk characterisation.

The data provided are considered sufficient to meet base set requirements for acute toxicity. Based on the oral LD_{50} values of 570-1377 mg/kg bw, AHTN should be classified as harmful if swallowed (Xn R 22). The dermal LD_{50}-values are >5000 mg/kg bw, so there is no need to classify AHTN for acute dermal toxicity.

Data for acute inhalation toxicity are not available.

AHTN has been tested in two dermal irritation studies in animals. In one study, no dermal effects were observed. In the other study as a 50% solution in diethyl phthalate (DEP), slight dermal irritation was observed with the solution as well as with DEP although the score for DEP was less. Based on recommended studies for hazard classification in rabbits, with the undiluted substance, AHTN does not need to be classified as a skin irritant. Dermal effects observed after topical application of AHTN in repeated dose toxicity studies may reflect (photo)-sensitisation, rather than irritation. Several sensitisation studies in humans showed no signs of dermal irritation by AHTN.

The photoirritation studies in animals indicate that AHTN is more irritating to the skin after irradiation with UV light. The results in human tests do not indicate a photoirritating effect in humans. Also, an *in vitro* phototoxicity test (in compliance with test guideline B.41 (EU/COLIPA Test)) was negative. No criteria for the classification of substances for photoirritation are available in Annex VI of Directive 67/548.

AHTN has been tested for ocular irritation in rabbits in two studies. In both studies, slight ocular irritation was observed. However, the magnitude of the effects is not high enough to require classification according to the EU guidelines.

No data on respiratory tract irritation are available.

The available data include sensitisation and photosensitisation studies in both animals and humans. The sensitisation studies with animals indicate some potential for sensitisation but the studies are only limitedly reported and were not done according to guidelines. Sensitisation studies in humans were negative.

In animal studies investigating photosensitising effects, mostly positive results were reported for AHTN, whereas negative results were reported in human studies on photosensitisation. It is to be noted that for this endpoint there is no validated test method available. The negative human data do not overrule the positive animal data, in line with 3.1.1 of Annex VI of Directive 67/548, which states that tests on man (human volunteers) should be discouraged and should not normally be used to negate positive animal data. Hence, it is concluded that AHTN is a photosensitiser. This may be due to photosensitising effects of AHTN itself, or to sensitising effects from photodegradation products arising from the interaction of AHTN and UV light. Evidence for the latter was obtained from a study where two of the four photodegradation products of AHTN reacted positive. This phenomenon may also explain the dermal effects observed in a dermal repeated dose toxicity study (see below).

In the absence of criteria for classification for photosensitisation in Annex VI of Directive 67/548, the need to communicate the photosensitising potential of AHTN to users can be dealt with by way of additional safety phrases and a Note, rather than applying R43. However, in the October 2006 meeting of the TC-C&L, the Commission stated that such a note will not be developed under the current legislation.

In a 28-day oral gavage study, no effects of AHTN were seen at doses up to and including 10 mg/kg bw/day.

In an adequate 90-day oral study, 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 the 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. Based on the marginal effects

observed at 15 mg/kg bw/day, the NOAEL is set at 5 mg/kg bw/day, which will be used in the risk characterization.

Three subchronic dermal studies of AHTN are available. In two of these, 13-weeks at 1, 10 and 100 mg/kg bw/day and 26-weeks at 0, 9, 18 and 36 mg/kg bw/day both applied unoccluded, the purpose was to screen AHTN for neurotoxicity against AETT as positive control. While clear evidence of neurotoxicity, both clinically and pathologically, was seen with the positive control AETT no such evidence for AHTN was found in either study at any dose level. Clear evidence of haematological and hepatotoxicity were seen at 100 mg/kg bw/day for 13 weeks and at 36 mg/kg bw/day for 26 weeks, however, because of the limited nature of the report, it is not possible to judge the severity of these effects. In the third study, AHTN was included only for comparison purposes at one dose level, which proved to be so irritating (possibly resulting from (photo)sensitisation) that the results with respect to systemic effects were confounded. In none of these studies is it possible to determine the actual doses received and because of the lack of collars the real route of exposure and no NOAEL could be established. Therefore, these studies are not used in the risk characterisation.

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

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

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, in an SOS chromotest with bacteria, in SCE and micronucleus tests with human cells 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 data available. AHTN is demonstrated to be non-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 further testing is needed.

No multigeneration study is available.

In an oral peri/postnatal toxicity study (exposure of the F_1-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. The exposure of F1 foetuses through mother's milk can be estimated based on a pharmacokinetic study with pregnant/lactating rats given oral doses of 2 and 20 mg 14C-AHTN/kg bw/day. Levels up to 1.89 and 25 mg AHTN equivalents (i.e. AHTN + metabolites)/l of whole milk were reported, for maternal oral doses of 2 and 20 mg/kg bw/d, respectively.

In an oral developmental study with rats, maternal toxicity occurred at 50 mg/kg bw/day. Developmental toxicity was not seen at the highest dose administered, 50 mg/kg bw/day. Therefore, the NOAEL for maternal toxicity can be established at 15 mg/kg bw/day. There is no evidence for developmental toxicity and the developmental NOAEL is ≥50 mg/kg bw/day, the highest dose administered. From the peri/postnatal study described above, a NOAEL of ≥20 mg/kg bw/day can be established for pup weight, pup survival and postnatal death, the

highest dose tested. These effects are not included in the oral developmental study. Since this NOAEL is also lower than the NOAEL for teratogenic effects generated during earlier periods of foetal development (50 mg/kg bw/day; see above), this NOAEL (≥20 mg/kg bw/day) will cover also these early teratogenic events. A NOAEL for developmental toxicity of ≥20 mg/kg bw/day will be taken forward to the risk characterization.

No effects on reproductive organs of male or female rats were seen in a 13-week oral study at doses up to 50 mg/kg bw/day (NOAEL ≥50 mg/kg bw/day).

AHTN has a very weak estrogenic potency *in vitro* but no such effects were seen *in vivo.*

4.3 RISK CHARACTERISATION

4.3.1 Workplace

Assuming that oral exposure is prevented by personal hygienic measures, the risk characterisation for workers is limited to the dermal and inhalation routes of exposure.
If applicable, quantitative risk assessment is performed by calculation of the MOS (the ratio between NOAEL/LOAEL and exposure levels) and comparison of this value with the minimal MOS. This minimal MOS is established via assessment factors, taking into account inter- and intraspecies differences, differences between experimental conditions and the exposure pattern of the worker, type of critical effects, dose-response relationship, confidence in the database, and correction for route-to-route extrapolation. A risk is indicated when the MOS is lower than the minimal MOS. In case of combined exposure the calculations are based on internal NOAELs and systemic exposure levels.

Acute toxicity

Inhalation exposure
There are no data on acute inhalation toxicity. Therefore, short term inhalation exposure has to be compared to available acute toxicity data for other routes. For clarity, potential risks are assessed for vapour as well as dust. Given the oral LD_{50} values of 570-1377 mg/kg bw and the dermal LD_{50} values of >5000 mg/kg bw and the highest anticipated exposure of 0.1 mg/m^3 to vapour in scenario 2 (Small size plants) during 0.15 hour per day, which is (0.25 h * 10m^3 / 8h * 0.1 mg/m^3) / 70 kg = 0.0005 mg/kg bw, it is concluded that there are no indications for concern with respect to acute toxicity by inhalation exposure of vapour **(conclusion ii)**.

Given the highest exposure for dust of 0.6 mg/m^3 during 2 h/d, which is (2 h * 10m^3 / 8h * 0.6 mg/m^3) / 70 kg = 0.021 mg/kg bw, in scenario 1 (for the incidental maintenance of the cooler) it is concluded that there are no indications for concern with respect to acute toxicity by inhalation exposure of dust **(conclusion ii).**

Dermal exposure
Given the dermal LD_{50} values of >5000 mg/kg bw and the highest anticipated exposure level of 39 mg/d (or 39 mg / 70 kg = 0.55 mg/kg bw) of a molten form, it is concluded that AHTN is of no concern for workers with regard to acute dermal effects **(conclusion ii)**.

Irritation and corrosivity

Skin irritation
- Acute dermal irritation
AHTN is not a skin irritant (**conclusion ii**).

- Corrosivity
AHTN is not corrosive to the skin (**conclusion ii**).

- Photoirritation
AHTN is not a photoirritant (**conclusion ii)**.

- Dermal irritation after repeated exposure
Based on the available data, AHTN is judged not to be a skin irritant. Hence, there is no concern for workers (**conclusion ii**).

Eye irritation

AHTN is not an eye irritant (**conclusion ii**).

Respiratory tract irritation
No data are available on local effects in the respiratory tract after acute exposure. Given the lack of skin and eye irritation potential, no significant respiratory irritation potential is expected (**conclusion ii**).

Sensitisation including photosensitisation

Sensitisation
AHTN is not a skin sensitiser (**conclusion ii**).

Photosensitisation
In animal studies a photosensitising potential was observed. In the four exposure scenarios workers may be exposed dermally to the following percentages of AHTN:

- Scenario 1: 100% AHTN (crystallisation);
- Scenario 2: 2% AHTN (compounding – all size plants – liquid); 100% (compounding – all size plants – dust); 100% (compounding – molten form);
- Scenario 3: 2% AHTN (handling); 0.002% AHTN (cleaning and maintenance);
- Scenario 4: 0.02% AHTN (handling).

Based on the available animal data (photosensitisation was observed from concentrations of 1% AHTN (lowest concentration tested)) and based on the % AHTN in the exposure scenarios, it cannot be excluded that photosensitising effects may occur in scenarios 1, 2 and 3 (handling) (**conclusion iii**).

The concern for photosensitisation for workers in scenario 3 (cleaning and maintenance) and scenario 4 is considered low, because the exposure concentration of AHTN in these scenarios (<1%) is below the general concentration limit normally applied for classification of preparations for sensitisation. Besides, negative results have been reported in human studies on photosensitisation with 1%, 5% and 10% AHTN preparations (**conclusion ii**).

In the absence of a risk phrase for photosensitisation, a specific Note can be used to warn workers for the photosensitising potential of AHTN. However, at the October 2006 meeting of the TC-C&L the Commission stated that such a Note will not be developed under the current legislation. If a specific Note to warn workers for the photosensitising potential of AHTN will be available, conclusion ii may be applicable for all scenarios.

Repeated dose toxicity

Inhalation exposure
The starting point for the risk assessment is the oral NOAEL of 5 mg/kg bw/day from the oral 90-day repeated dose study with rats. Assuming an oral absorption value of 50% for rats, this NOAEL corresponds to an internal no-effect dose of 2.5 mg/kg bw/day. For exposure after inhalation no data are available, the absorption is assumed to be 100%.

The minimal MOS value is calculated to be 100[2]. Comparing the MOS values (≥269) with the minimal MOS value, it is concluded that there is no concern for workers with regard to the repeated inhalation exposure (**conclusion ii**).

[2] Minimal MOS inhalation repeated dose toxicity (100) = 4*2.5 (interspecies) x 5 (intraspecies) x 2 (semichronic

Dermal exposure
The starting point for the risk assessment is the oral NOAEL of 5 mg/kg bw/day from the oral 90-day repeated dose study with rats. Assuming an oral absorption value of 50% for rats, this NOAEL corresponds to an internal no-effect dose of 2.5 mg/kg bw/day. Although it is recognized that quite different dermal exposure conditions exist between the different scenarios, e.g. in terms of exposure times and area doses, a value of 4.1% is taken for dermal absorption in all worker scenarios.

The minimal MOS value is calculated to be 100[3]. Comparing the MOS values (≥109) with the minimal MOS value, it is concluded that there is no concern for workers with regard to the repeated dermal exposure (**conclusion ii**).

Combined exposure
The total body burden is determined by uptake after dermal as well as exposure by inhalation of AHTN. This combined exposure should not be applied if a simultaneous exposure can be excluded. Combination of various exposure routes is only relevant for the crystallisation in scenario 1 (total internal body burden of 0.0102 mg/kg bw/d) and the compounding in scenario 2 (total internal body burden of 0.0057 and 0.0131 mg/kg bw/d for large and medium size plants and small size plants, respectively). The resulting MOS values are 245, 438, and 190 for crystallisation and compounding in large and medium size plants and small size plants, respectively. Comparing these MOS values with the minimal MOS value (100), **conclusion ii** is proposed for all three scenarios where combined (dermal and inhalation) exposure is relevant.

Mutagenicity

AHTN is a non-genotoxic substance (**conclusion ii**).

Carcinogenicity

ATHN lacks liver tumour initiating and promoting activity in rats when exposed to human-relevant doses. There are no other carcinogenicity data available. The mutagenicity data on AHTN do not indicate a concern with regard to carcinogenicity nor does AHTN possess any structural features that would raise a concern (**conclusion ii).**

Toxicity for reproduction

Effects on fertility
No multigeneration study is available. There are no indications for effects on fertility in the oral 90-day study with rats (this study investigation was limited to histological examination of the reproductive organs). No adverse effects were reported up to the highest dose tested (NOAEL ≥50 mg/kg bw/day).

to chronic extrapolation)

[3] Minimal MOS dermal repeated dose toxicity (100) = 4*2.5 (interspecies) x 5 (intraspecies) x 2 (semichronic to chronic extrapolation)

Dermal exposure
Inhalation and dermal developmental studies are lacking.

In an oral developmental study with rats, maternal toxicity occurred at 50 mg/kg bw/day. Developmental toxicity was not seen at the highest dose administered, 50 mg/kg bw/day. The peri/postnatal study, including endpoints as pup weight, pup survival and postnatal death, resulted in a NOAEL (highest dose level) of ≥20 mg/kg bw/day. Therefore, the NOAEL for maternal toxicity can be established at 15 mg/kg bw/day assuming 50% oral absorption (internal no-effect dose 7.5 mg/kg bw/d). There is no evidence for developmental toxicity and the developmental NOAEL is ≥20 mg/kg bw/day (internal no-effect dose ≥10 mg/kg bw/d), the highest dose administered. AHTN has a very weak estrogenic potency *in vitro* but such effects were not seen *in vivo*.

Given the lowest internal no-effect dose (7.5 mg/kg bw/d) and the highest internal body burdens of 0.0093 mg/kg bw/d (scenario 2) for inhalation exposure and 0.023 mg/kg bw/d (scenario 2) for dermal exposure, the resulting MOS values are 806 and 326, respectively. For combined exposure (dermal and inhalation), the highest combined internal body burden of 0.0131 mg/kg bw/d results in a MOS of 572. A minimal MOS of 50 is considered appropriate for this effect. The latter is established by taking into account an interspecies factor of 10 (4 for metabolic size differences * 2.5 for remaining differences) and an intraspecies factor of 5. Comparison of the calculated MOS values with the minimal MOS value leads to **conclusion ii** for all scenarios.

4.3.2 Consumers

The starting point for the risk characterisation is the external dermal exposure level of 0.34 mg/kg bw/day together with the inhalatory exposure level of 0.0046 mg/kg bw/day. Because the absorption of AHTN through human skin is 4.1% (worst-case assumption), the external dermal exposure level results in an internal exposure level of 0.014 mg/kg bw/day. For inhalation, 100% absorption is assumed, so the internal exposure level is 0.0046 mg/kg bw/day. The total internal exposure amounts 0.019 mg/kg bw/day.

Irritation

The available data on AHTN do not indicate a skin irritating or photoirritating potential. Hence, there is no concern for consumers for skin (photo-)irritation (**conclusion ii)**.

There is no concern for consumers for eye irritation, because AHTN is not an eye irritant (**conclusion ii)**.

No data are available on local effects in the respiratory tract. However, given the lack of skin and eye irritation potential, no significant respiratory irritation potential is expected. (**conclusion ii**).

Sensitisation

Whereas the available data do not indicate a skin sensitising potential of AHTN (**conclusion ii)**, a photosensitising potential was identified in animal studies. The concern for consumers

for photosensitisation, however, is low, because the concentration of AHTN in consumer products (<1%) is below the general concentration limit normally applied for classification of preparations for sensitisation. Besides, negative results have been reported in human studies on photosensitisation with 1%, 5% and 10% AHTN preparations (**conclusion ii**).

Repeated dose toxicity

The starting point for the risk assessment is the oral NOAEL of 5 mg/kg bw/day from the 90-day study with rats. Assuming an oral absorption value of 50% for rats, this NOAEL corresponds to an internal no-effect dose of 2.5 mg/kg bw/day.

Comparing this internal no-effect dose with the calculated human systemic exposure level of 0.019 mg/kg bw/day, a margin of safety (MOS) of 132 can be calculated. Using assessment factors of 10 for intra- and interspecies (2.5 x 4) differences, a factor of 2 for duration extrapolation and a factor of 1 for dose-response, the minimal MOS would be 200. However, it should be taken into account that the NOAEL is set rather conservatively, given the marginal effects observed at 15 mg/kg bw/day. Taking also into account the worst-case character of the exposure estimate, the MOS of 132 indicates no concern for consumers following repeated dermal exposure (**conclusion ii).**

Mutagenicity

AHTN is a non-genotoxic substance (**conclusion ii).**

Carcinogenicity

ATHN lacks liver tumour initiating and promoting activity in rats when exposed to human-relevant doses. There are no other carcinogenicity data available. The mutagenicity data on AHTN do not indicate a concern with regard to carcinogenicity nor does AHTN possess any structural features that would raise a concern (**conclusion ii).**

Reproductive toxicity

In an oral developmental toxicity study with rats, developmental toxicity did not occur at maternal toxic dose levels ($NOAEL_{developmental\ toxicity}$ ≥50 mg/kg bw/day, $NOAEL_{maternal\ toxicity}$ 15 mg/kg bw/day). A peri/postnatal study with rats, including endpoints such as pup weight, pup survival and postnatal death, resulted in a NOAEL for developmental toxicity of ≥20 mg/kg bw/day (the highest dose tested). Assuming an oral absorption value of 50% for rats, this $NOAEL_{developmental\ toxicity}$ corresponds to an internal no-effect dose of ≥10 mg/kg bw/day.

Comparing this internal no-effect dose with the calculated human systemic exposure level of 0.019 mg/kg bw/day, a MOS of 526 can be calculated. This MOS indicates no concern for consumers for developmental toxicity (**conclusion ii)**, based on comparison with a minimal MOS of 100, taking into account intra- (factor of 10) and interspecies differences (factor of 10 (2.5 x 4)) and the lack of effect at the highest dose tested (factor of 1 for dose-response).

For consumers, **conclusion ii** is reached for all endpoints.

4.3.3 Man indirectly exposed via the environment

For man exposed via the environment the inhalation and oral route are applicable. The contribution of the inhalation of AHTN via air is negligible compared to other uptake routes, hence only the main oral exposure route via fish and root crops is taken into account. Because of the occurrence of AHTN in mother's milk, a separate risk characterization is necessary for breast-fed babies.

Exposure via food and water

Using EUSES, the total daily intake is estimated at 1.8 µg/kg bw/day for the local scenario (large/medium compounding scenario) and 0.012 µg/kg bw/day for the regional scenario.

Repeated dose toxicity

The starting point for the risk assessment is the oral NOAEL of 5 mg/kg bw/day from the oral 90-day repeated dose study with rats. Assuming an oral absorption value of 50% for rats, this NOAEL corresponds to an internal no-effect dose of 2.5 mg/kg bw/day. Using assessment factors of 10 for intra- and interspecies (2.5 x 4) differences, a factor of 2 for duration extrapolation and a factor of 1 for dose-response, the minimal MOS would be 200. For both local and regional scenario's, the margin of safety is higher than the minimal MOS (1389 and 2.1E+05, respectively), which results in a (**conclusion ii).**

Carcinogenicity

ATHN lacks liver tumour initiating and promoting activity in rats when exposed to human-relevant doses. There are no other carcinogenicity data available. The mutagenicity data on AHTN do not indicate a concern with regard to carcinogenicity nor does AHTN possess any structural features that would raise a concern (**conclusion ii**).

Reproductive toxicity

In an oral developmental toxicity study with rats, developmental toxicity did not occur at maternal toxic dose levels ($NOAEL_{developmental\ toxicity}$ ≥50 mg/kg bw/day, $NOAEL_{maternal\ toxicity}$ 15 mg/kg bw/day). A peri/postnatal study with rats, including endpoints such as pup weight, pup survival and postnatal death, resulted in a NOAEL for developmental toxicity of ≥20 mg/kg bw/day (the highest dose tested). Assuming an oral absorption value of 50% for rats, this $NOAEL_{developmental\ toxicity}$ corresponds to an internal no-effect dose of ≥10 mg/kg bw/day. Comparing this internal no-effect dose with the local and regional values, MOSses of 5555 and 8.3E+5 respectively can be calculated. These MOSses indicate no concern for humans exposed indirectly via the environment for developmental toxicity (**conclusion ii)**, based on comparison with a minimal MOS of 100, taking into account intra- (factor of 10) and interspecies differences (factor of 10 (2.5 x 4)) and the lack of effect at the highest dose tested (factor of 1 for dose-response).

Exposure via mother's milk

An analysis of the milk from 59 nursing mothers revealed the presence of AHTN with a mean value of 112 µg/kg milk fat. The minimum and maximum values found were undetectable and 565 µg/kg milk fat, respectively (the highest mean and maximum levels from the entire data

base). A fat content ranging from 1.5 to 4.2% was also reported. Based on the highest fat content (worst case), human milk contains 4.7 µg/kg whole milk (mean) or 23.7 µg/kg whole milk (maximum). In an oral peri/post natal study in which female rats were exposed orally to AHTN from day 14 of gestation through weaning, there were no effects on the dams at maternal doses of up to 20 mg/kg bw/day or on the pups which were exposed via the milk during nursing. Measurements of levels of AHTN (9.4 and 2.1 µg/ml at 4 or 8 hr post dosing, respectively; parent AHTN only) in the milk of the dams dosed at 20 mg/kg bw/day compared to the levels found in human milk samples indicate that the pups in the high dose group were exposed to levels approximately 460 to 2000 times the mean level. This corresponds to approximately 90 to 400 times the maximum level found in human milk samples (4.7 and 23.7 µg AHTN/kg whole milk, respectively).

Even for the highest concentration observed in human milk samples, compared to the highest concentration in rat milk, a sufficiently high MOS can be calculated (~100). Taking into account that at the top maternal dose no effects were observed at all (i.e. the real NOAEL is at least equal but probably above this top dose), a **conclusion ii** is reached.

Additional to the assessment above, which is only based on concentrations in human *versus* rat milk, an assessment is carried out which also takes into account, the amount of milk that is consumed by infants and rat pups, in a way similar to the assessment applied in the Risk Assessment Report on MCCP. This assessment results in a difference of approximately 1000 between the levels of AHTN exposure in the rat study (in which no adverse effects were found) and human infant exposure. This large Margin of Safety (MOS) leads to little cause for concern and thus a **conclusion ii**.

A **conclusion ii** was reached for man exposed indirectly via the environment at the local scale as well as at the regional scale, and also for breast-fed babies.

4.3.4 Combined exposure

A worst case estimate for the combined (internal) exposure to AHTN would be the sum of the worst case estimates for the three individual populations, i.e. 0.023 mg/kg bw/day (dermal, scenario 2 compounding “molten, for workers) + 0.019 mg/kg bw/day (dermal and inhalation, consumers) + 0.0018 mg/kg bw/day (oral and inhalation, locally via the environment). This results in a total internal (worst case) combined exposure estimate of 0.044 mg/kg bw/day. The contribution of the exposure via the environment attributes only about 4%. The contribution to the total exposure as worker or as consumer is about equal. This value is compared to the two relevant chronic endpoints, namely repeated dose toxicity and reproductive toxicity.

Comparing this value to an internal no-effect dose of 2.5 mg/kg bw/day from the repeated dose toxicity study, a MOS of 57 can be derived. Based on a comparison with a minimal MOS of 100 (established by taking into account an interspecies factor of 10 (4 for metabolic size differences * 2.5 for remaining differences), an intraspecies factor of 5 for workers and a factor of 2 for semichronic to chronic exposure extrapolation, is considered a borderline case. However, given the worst case approaches taken in both exposure (worker and consumer) assessments, this MOS is also considered acceptable (**conclusion ii**).

Comparing this value to an internal no-effect dose of ≥10 mg/kg bw per day for maternal toxicity, a MOS of ≥ 294 can be derived. A minimal MOS of 50 is considered appropriate for this effect. The latter is established by taking into account an interspecies factor of 10 (4 for metabolic size differences * 2.5 for remaining differences) and an intraspecies factor of 5 for worker. Comparison of the calculated MOS values with the minimal MOS value leads to **conclusion ii** for workers after total combined exposure (no concern).

4.3.5 Physico-chemical properties

Based on the available information, AHTN is not flammable, not explosive and not oxidising. Therefore, AHTN is expected to be of no concern for human health regarding physico-chemical properties (**conclusion ii**).

5 RESULTS

5.1 ENVIRONMENT

Aquatic compartment (incl. sediment)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, compounding, formulation and private use.

Terrestrial compartment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, compounding, formulation and private use.

Atmosphere

As no $PNEC_{air}$ could be derived, a risk characterisation for the atmosphere is not possible.

Secondary poisoning

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

This conclusion applies to production, compounding, formulation and private use.

5.2 HUMAN HEALTH

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) is reached because it cannot be excluded that photosensitising effects may occur in scenarios 1, 2 and 3 (handling).

In the absence of a risk phrase for photosensitisation, a specific Note can be used to warn workers for the photosensitising potential of AHTN. However, at the October 2006 meeting of the TC-C&L the Commission stated that such a Note will not be developed under the current legislation. If a specific Note to warn workers for the photosensitising potential of AHTN will be available, conclusion ii may be applicable.

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Humans exposed via the environment

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Combined exposure

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

GLOSSARY

Standard term / Abbreviation	Explanation/Remarks and Alternative Abbreviation(s)
AF	assessment factor
Ann.	Annex
BCF	bioconcentration factor
bw	body weight / *Bw*, *b.w.*
°C	degrees Celsius (centigrade)
CAS	Chemical Abstract System
CEC	Commission of the European Communities
CEN	European Committee for Normalisation
CEPE	European Council of the Paint, Printing Ink and Artists' Colours Industry
d	day(s)
DG	Directorate General
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{50lab}	period required for 50 percent dissipation under laboratory conditions (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
$DT_{90field}$	period required for 90 percent dissipation under field conditions (define method of estimation)
dwt	dry weight / dw
EC	European Communities
EC	European Commission
EC_{50}	median effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
EU	European Union
EUSES	European Union System for the Evaluation of Substances
f_{oc}	Fraction of organic carbon
g	gram(s)
GLP	Good Laboratory Practice
h	hour(s)

Standard term / Abbreviation	Explanation/Remarks and Alternative Abbreviation(s)
ha	Hectares / *h*
HPLC	High Pressure Liquid Chromatography
IARC	International Agency for Research on Cancer
IC_{50}	median immobilisation concentration or median inhibitory concentration 1 / *explained by a footnote if necessary*
ISO	International Standards Organisation
IUPAC	International Union for Pure Applied Chemistry
kg	kilogram(s)
K_{oc}	organic carbon adsorption coefficient
K_{ow}	octanol-water partition coefficient
Kp	Solids water partition coefficient
kPa	kilo Pascals
l	litre(s)
$L(E)C_{50}$	Lethal Concentration, Median
LEV	Local Exhaust Ventilation
log	logarithm to the basis 10
µg	microgram(s)
m	Meter
MAC	Maximum Accessibility Concentration
mg	milligram(s)
MOS	Margins Of Safety
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
Pa	Pascal unit(s)
PEC	Predicted Environmental Concentration
pH	potential hydrogen -*logarithm* (to the base 10) of the hydrogen ion concentration $\{H^+\}$
pKa	-*logarithm* (to the base 10) of the acid dissociation constant

Standard term / Abbreviation	Explanation/Remarks and Alternative Abbreviation(s)
pKb	-*logarithm* (to the base 10) of the base dissociation constant
PNEC(s)	Predicted No Effect Concentration(s)
$PNEC_{water}$	Predicted No Effect Concentration in Water
(Q)SAR	Quantitative Structure Activity Relationship
STP	Sewage Treatment Plant
STP	Sewage Treatment Plant
TGD	Technical Guidance Document[4]
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products or Biological material
v/v	volume per volume ratio
w/w	weight per weight ratio
WWTP	Waste Water Treatment Plant

[4] Commission of the European Communities, 1996. Technical Guidance Documents in Support of the Commission Directive 93/67/EEC on risk assessment for new substances and the Commission Regulation (EC) No 1488/94 on risk assessment for existing substances. Commission of the European Communities, Brussels, Belgium.
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The report provides the comprehensive risk assessment of the substance 1-(5,6,7,8-TETRAHYDRO-3,5,5,6,8,8-HEXAMETHYL-2-NAPTHYL)ETHAN-1-ONE (AHTN). It has been prepared by The Netherlands in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. The environmental risk assessment concludes that there is no concern for any of the environmental compartments.

For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified. The human health risk assessment concludes that there is concern for workers with regard to photosensitising effects. For consumers, for humans exposed via the environment and for human health (physico-chemical properties) there is no concern.