1,3,4,6,7,8-HEXAHYDRO-4,6,6,7,8,8-HEXAMETHYLCYCLOPENTA-γ-2-BENZOPYRAN

(1,3,4,6,7,8-HEXAHYDRO-4,6,6,7,8,8-HEXAMETHYLIN-DENO[5,6-C]PYRAN - HHCB)

CAS No: 1222-05-5

EINECS No: 214-946-9

SUMMARY RISK ASSESSMENT REPORT

Final report, 2008

The Netherlands

FINAL APPROVED VERSION

Rapporteur for the risk assessment of HHCB 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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Final report:	**2008**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance HHCB 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.

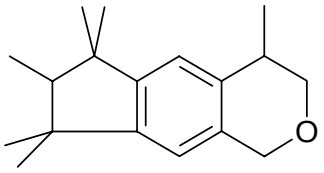
For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be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

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

CONTENTS

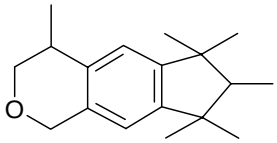
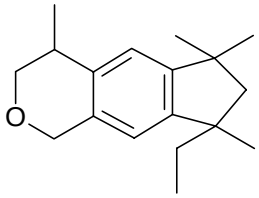
1 GENERAL SUBSTANCE INFORMATION

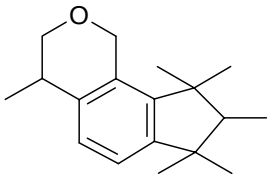
1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number:	1222-05-5
EINECS Number:	214-946-9
IUPAC Name:	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylcyclopenta-γ-2-benzopyran
Synonyms:	1,3,4,6,7,8-Hexahydro-4,6,6,7,8,8-hexamethylindeno(5,6-c)pyran (EINECS name) HHCB Abbalide Chromanolide Pearlide Galaxolide
Molecular weight:	258.41
Molecular formula:	$C_{18}H_{26}O$
Structural formula:	

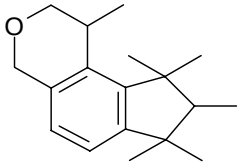
1.2 PURITY/IMPURITIES, ADDITIVES

Purity: Sum of isomers with typical composition ≥ 95% w/w

CAS No 1222-05-5 Main isomer	74-76%	1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethyl-cyclopenta-γ-2-benzopyran 
CAS Nos 78448-48-3 and 78448-49-4:	6-10%	1,3,4,6,7,8-hexahydro-4,6,6,8-tetramethyl-(6 or 8)-ethylcyclopenta- γ -2-benzopyran 
CAS No 114109-63-6:	5-8%	1,3,4,7,8,9-hexahydro-4,7,7,8,9,9-hexamethyl-cyclopenta [H]-2-benzopyran



CAS No 114109-62-5:	6-8%	1,2,4,7,8,9-hexahydro-1,7,7,8,9,9-hexamethyl-cyclopenta[F]-2-benzopyran, 6-8%



Impurities:

	<1%	1,1,2,3,3-pentamethyl-5-t-pentylindan
	<1%	1,1,2,3-tetramethyl-5-t-butyl-3-ethylindane
CAS No 1217-08-9, EINECS No 214-934-3	<1%	β,1,1,2,3,3-hexamethylindan-5-ethanol
CAS No 66553-13-7	<1%	5-t-butyl-1,1,2,3,3-pentamethylindan
CAS No 1203-17-4, EINECS No 214-868-5	<1%	1,1,2,3,3-pentamethylindan,

Additives: none

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value	Comments
Physical state	viscous liquid	
Melting point	-10 - 0 °C	determined by cooling to –30 °C and gradual warm up
Boiling point	160 °C at 4 mm Hg (325 °C at 760 mm Hg)	recorded in the distillation of HHCB in manufacturing plant. (conform mathematical conversion into 330 °C at 760 mm Hg) Stein and Brown method MpBp calculated : 325 degree °C, at 760 mm Hg (162 °C at 4 hPa)
Relative density	0.99 – 1.015 g/cm^3 at 20 °C	oscillating densitometer, OECD TG 109
Vapour pressure	0.0727 Pa at 25 °C (s.d. 0.0123 Pa)	gas saturation method, OECD TG 104, ^{14}C-labelled material
Water solubility	1.75 mg/l at 25 °C (1.99 mg/l at pH 5; 1.65 mg/l at pH 7; 1.69 mg/l at pH 9) # 0.4 mg/l 2.3 (±0.14) mg/l	flask method (FDA 1987) similar to OECD TG 105, ^{14}C-labelled material Calculation (SRC) column elution method
Partition coefficient n-octanol/water (log value)	5.9 6.26 5.74 5.3 #	reversed-phase HPLC, OECD TG 117 calculation calculation slow stirring method
Granulometry	not applicable	
Flash point	>100 °C	closed cup, Pensky Martens Dir. 84/449/EEC, A.9
Autoflammability	> 200 °C	Estimated, based on structure and physical data comparison.
Flammability	non flammable	not a flammable liquid.It is a combustible liquid which can burn.It has no pyrophoric properties
Explosive properties	not explosive	calculated, CHETAH, v. 7.0
Oxidizing properties	not oxidizing	indication from structure and experience
Henry's constant	36.9 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: N

R-phrases: R50/53

S-phrases: S60, 61

2 GENERAL INFORMATION ON EXPOSURE

Production

The entire production of HHCB is at one plant in Europe, with a production volume in 2000 between 1000 and 5000 ton/y (HHCB undiluted). Circa 63% of the production volume (HHCB undiluted) is exported outside the EU (that is the EU-15, and including also Norway and Switzerland), of which 25% (HHCB undiluted) in form as undiluted and 37.5% (HHCB undiluted) after dilution. To simplify handling nearly all of the HHCB produced is diluted in organic solvent to a 65% by weight pourable but still highly viscous liquid. This dilution is carried out at another plant in Europe. A relatively small portion of HHCB, about <500 ton is also diluted at the plant where it is produced.

Uses

The pourable liquid 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. HHCB is the 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 HHCB is mixed. Applications of the fragrance oils are in consumer products such as perfumes, cosmetics, soaps, shampoos, detergents, fabric conditioners, household cleaning products and air fresheners.

In Europe there are approximately 39 compounding sites of circa 29 larger and medium sized companies that receive HHCB. A fraction of the production is directly used in bulk formulation of consumer products, such as the preparation of detergents by the larger producers. The fraction directly used is estimated at 14%.

For the exposure calculations for the life-cycle part 'private use' the volume reported by IFRA for 2000 of 1427 ton will be used. HHCB is applied in consumer products, mainly in cleaning agents, but also in cosmetics. An analysis was made of the regional differences of the use throughout the EU-15 member states. 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-15, 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 HHCB *per capita* in Europe. A ‘cultural’ factor of different use volumes of detergents may cause a higher use of detergents per capita by a 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 a factor of 1.5 as compared to the average *per capita* use of HHCB. As both factors are independent, the combination gives a factor 1.25 · 1.5 = 1.88 above the average use in a 'worst case regional scenario for southern Europe' for the year 2000.

For 2000 an evenly distributed use would mean 1427 ton/370 million inhabitants (3.86 g *per capita* per year) and to cover the uneven use in a realistic worst case scenario this would be 1.88 · 3.86 = 7.23 g *per capita* per year. In the northern countries the minimum use volume would be the maximum/3.3 = 7.23/3.3 = 2.2 g *per capita* per year, whereas there the highest level would theoretically be 1.0 · EU-average = 3.86 g *per capita* per year. According to the TGD, 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 7.14 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

Site	Volume of HHCB undiluted, kg/yr	# of working days per year	Emission factor after treatment,%	Conc. in influent to STP, µg/l	PECsurface water, µg/l
Production	1000 – 5000 ton	330	-	10	0.66
Comp. 1	143,000	240	0.02	46	0.078
Comp. 2 (year: 2006)	391,000	312	0.018	3.4	0.738
Comp. 3	223,569	250	0.016 – 0.048	13	0.007
Comp. 4	107,315	250	0.06	95 (WWTP)	0.026
Comp. 5	43,914	250	0.008 – 0.002	0.16	0.04
Comp. 6	187,000	250	0.00	0	
Comp. 7 – Generic scenario for a large/medium site	17,600	250	0.06 *	21 #	0.526
Comp. 8 – Generic scenario for a small site	2,140	250	0.2 **	8.6 #	0.232
Large formulator	50,000	345	0.017	12.3	0.32
Generic small formulator	6,135	250	0.2 #	24.5	0.58

* 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 HHCB in end product formulation in Europe for 2000 is assumed to be 1427 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 1427 ton minus the 14% sold directly to the formulators, thus 1227 ton/year. Assuming 1000 formulation sites in the EU-15+2, the use of HHCB on a small formulator site is 1227 ton / 1000 = 1.227 ton per year. For the assessment of a 'reasonable worst case, this use volume is multiplied by a factor of 5: Thus, 1.227 · 5 = 6135 kg/year (or

0.4% of the 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 49 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 HHCB used in compounding fragrances in Europe for 2000, i.e. 1427 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 19.6 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, HHCB 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 3.7 hours.

In a primary biodegradation process. HHCB is rapidly transformed to a series of more polar metabolites, with HHCB-lactone and hydroxycarboxylic acid as likely intermediates. 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 HHCB the parent substance was transformed to a series of polar metabolites. HHCB disappeared with half-life values of 10 – 15 hours. In the river die-away test HHCB disappeared with a half-life of 100 hours and the biological degradation was 60% in 28 days. Field measurements on sludge amended soil indicate HHCB disappeared almost completely from soil within one year. The half-life based on unfrozen conditions in sludge amended soil studies was around 140 - 145 days. The residues in soil after one year ranged from below 10% to 14% of the initial concentrations. The half-life of 105 days in the sludge amended soil test is of course most relevant for the fate of HHCB in soil in the EUSES model, whereas 79 days was noted for the sediment. Subsequently, for the environmental risk assessment, HHCB may be considered as 'inherently biodegradable, not fulfilling criteria' (terminology of the EU-TGD, EC 2003). For surface water, sediment and soil, the PECs will be calculated using conservative biodegradation rate constants expressed as half-life times: 60 d in surface water (20 ºC) and 150 d in the soil and sediment compartments (12 ºC).

A K_{oc} value for HHCB can be estimated from the K_{ow} value of 5.3 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 4.39 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 0.0727 Pa and a water solubility of 1.75 mg/l a Henry's Law Constant of 10.7 $Pa.m^3/mol$ is calculated. The Henry's Law Constant was empirically determined at 36.9 $Pa.m^3/mol$. The latter was used in the PEC calculations.

According to the SimpleTreat model, HHCB 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} = 5.3 and k_{biodeg} = 0, the fate of HHCB predicted by EUSES is 10.4, 22.4 and 67.2% in air, water and sludge, respectively. The available studies are not conclusive on the quantitation of the biodegradation of HHCB in an STP. Therefore the EUSES model is used for local industrial scenarios whereas the estimation of PEClocal for consumer use is based on the concentrations measured in effluent and sludge in recent monitoring programs.

The bioconcentration in fish was studied in various experiments. A GLP-study was carried out according to OECD Guideline 305E. Bluegill sunfish (*Lepomis macrochirus*) were exposed in a flow-through system to two concentrations of radio labelled HHCB. The fish were exposed for 28 days; the elimination period was also 28 days. The concentration of HHCB 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 2 - 3 days for HHCB, allowing calculation of the rate constant for elimination (k_2). Based on the concentration of parent material, the BCF for the whole fish was 1584, which is used for the environmental risk assessment.

The bioconcentration of HHCB 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. For *C. riparius* the result was given as log BCF = 1.93 to 2.14; for the worm the result was log BCF = 3.43 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. It is calculated that BCFworm is 2395 $l.\ kg^{-1}$. Transfer coefficients were determined in lettuce and carrots growing on sludge amended soil samples. It is concluded under normal conditions that transfer of HHCB from the soil to plants is not relevant.

Most concentration measurements are based on analysis of the main isomer and its calibration to a reference sample (HHCB technical). Available studies indicate that the ratio of the main isomer versus other isomers in environmental samples is the same as in the reference HHCB technical sample.

The main isomer of HHCB consists of two diastereomers each with 2 enantiomers. In general the 4 enantiomers occur in the environmental samples in the same ratio as in the technical HHCB mixture. Selective transformation of the G1 enantiomer was observed in one fish species (an order of magnitude difference). The selectivity towards G2 and G3 was lower. In 4 other fish species and in zebramussels minor to no selective transformation was observed.

Toxicity and ecotoxicity studies have been carried out with HHCB technical. As the ratios in the environment are generally the same as in the HHCB technical, no recalculation or correction for other isomer ratios 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 19.6 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 HHCB 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 just above the observed 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 = 87.5 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 Scenario (90^{th}-percentile, 1.4 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, 4.7 µg/l). This level is comparable to the recently reported data from Austria and Sweden, which are also in line with the Northern EU-15 Scenario. The maximum of 9.4 µg/l observed in Spain is above the 90^{th}-percentile of Southern EU-15 by a factor of 2. For the risk characterisation the Southern EU-15 Scenario is used: **PECeffl = 4.7 µg/l (total).**

The concentration in sludge predicted by the TGD regional (10%) scenario = 665 mg/kg dwt. For the Northern EU-15 Scenario the calculations were made using the 90^{th}-percentile of recent data for Germany: 11.5 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, 46.9 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 factor of 10. For the risk assessment the Southern EU-15 Scenario will be used: **$PEClocal_{water}$ = 0.49 µg/l.** The 90^{th}-percentile of the surface water samples in the high effluent input area in Berlin (1996/1997) was 2.73 µg/l.

The predictions based on the current effluent and sediment concentrations predict the current 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: **$PEClocal_{sediment}$ = 0.262 mg/kg wwt ~ 1.21 mg/kg dwt.**

Terrestrial compartment

The predicted concentrations in agricultural soil after 10 years of sludge application are 0.014 and 0.06 mg/kg dwt for the Northern and the Southern EU-15 Scenarios. 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 HHCB/kg after one month. 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. The concentrations found in the floodplains of the river Elbe were below 0.01-0.02 mg/kg. 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: **$PEClocal_{soil}$ = 0.06 mg/kg wwt.**

Atmosphere

The concentrations observed in ambient air in Norway are below PECregional air. The concentrations over Lake Michigan were below PEClocal in the SEU scenario and just above PECregional for NEU (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 13 and 37 ng/l of rain, the deposition is 0.025 - 0.071 $\mu g/m^2/d$. These results are above the total deposition flux estimated for The Netherlands by a factor of 4 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. HHCB 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 the Czech fish are below the fish from the high effluent input area in Berlin by a factor of 10. This confirms that all fish reports other than from the high effluent input area in Berlin are below $PECoral_{fish}$ for the Southern European Scenario (0.41 mg/kg wwt). It had 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 also the levels in fish have been reduced considerably. No recent data are available for comparison with the Northern European Scenario (0.11 mg/kg wwt). For the risk assessment the Southern EU-15 Scenario will be used, since it covers all monitoring data except for some historic extremes in the Berlin area: **$PECoral_{fish}$ = 0.41 mg/kg wwt.** The 90^{th}-percentile for all fish in the Berlin area (1996/1997) was 1.50 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 formulatiors in the EU, the treatment of waste water in a sewage treatment plant is common practice. As the fraction discharged with the effluent is 0.224 (according to EUSES), the values after treatment are roughly 0.224 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 3.2.

Table 3.2 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)	0.00286	0.206	0.111	0.165	0.0367
Compounding Site 8 (Small generic)	0.00286	0.085	0.046	0.070	0.0175
Formulation Large company	0.00286	0.122	0.066	0.099	0.0234
Formulation generic	0.00286	0.237	0.128	0.190	0.0416
Private use					
TGD regional (10%)	0.0331	0.877	0.472	0.721	0.1861
southern EU-15	0.00286	0.048	0.0261	0.040	0.0117
northern EU-15	0.000367	0.0137	0.0074	0.011	0.0027

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, concentration-response, variability of replicates, control survival, etc.). Based on the results of the tests the lowest value is the EC_{10} of is 0.044 mg/l for the larval development of the marine crustacean *Acartia tonsa*. Therefore with an assessment factor of 10, **$PNEC_{water}$ is 4.4 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 20 mg/l. With an assessment factor of 10, the **$PNEC_{STP}$** would be > 2 mg/l. This PNEC is above the water solubility of HHCB of 1.75 mg/l.

PNECsediment is determined from the results of the three tests, with the midge larvae, amphipoda 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 a sediment containing 5% organic carbon and thus NOEC needs to be standardised to 5% organic carbon. The

lowest NOEC is 19.7 mg/kg for the growth of *Hyalella azteca*. 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 **2.0 mg/kg dwt.** Based on the equilibrium partitioning theory, **$PNEC_{sediment, EqP}$ = 10.9 mg/kg dwt**. The $PNEC_{sediment}$ based on sediment toxicity tests and the one derived by equilibrium partitioning from $PNEC_{water}$ differ by a factor of 5.5.

Terrestrial compartment

No data are available on the toxicity to plant and specific microorganisms in soil. Two long term tests with earthworms and springtails 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, $PNEC_{soil, equil}$ = 1.28 mg/kg wwt or 1.54 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 HHCB. A NOAEL of 150 mg/kg bw/d was derived from a 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 3000 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 a $PNEC_{oral}$ = 33.3 mg/kg food. In a 21-day reproduction and development toxicity study, the NOAEL was 50 mg/kg/d. With the same conversion as above, the NOEC in food is 1000 mg/kg. The assessment factor for a 28 day test is 300 and then the result is 3.33 mg/kg food: **Thus $PNEC_{oral}$ ranges from 33.3 to 3.33 mg/kg food.** In the current risk assessment $PNEC_{oral}$ = 3.33 mg/kg food was used.

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 44 µg/l for the marine copepod *Acartia tonsa*. Therefore the **$PNEC_{marine\ water}$ = 0.44 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 4.3 mg/kg wwt (OC-normalised). Thus **$PNEC_{marine\ sediment}$ = 0.086 mg/kg wwt or 0.394 mg/kg dwt.**

Other effects

Other effects reported in literature include endocrine interaction 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 3.3.1. The PNECs used are > 2000 mg/l for the STP and 4.4 µg/l for aquatic organisms. $PNEC_{sediment}$ = 0.43 mg/kg wet weight or 2.0 mg/kg dry weight is derived directly from toxicological data, where the intake of HHCB 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 done for the sediment in the Teltow Canal which was a cause for concern in earlier risk assessments. Recently measured levels show that PEC/PNEC is below 1. For completeness the measurements in Berlin in 1996/1997 are included. In the tiered approach taken in this risk assessment report the availability of sediment toxicity data has generated a higher PNEC value, now resulting in a ratio below 1 also for these historic samples.

All 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 3.3. PNECsoil is 0.31 mg/kg dwt or 0.28 mg/kg wwt. 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 3.3 mg/kg. This PNEC is compared with PEC_{oral} for fish as well as for worms. The PECs for private use are 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 3.3.

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

Table 3.3. PEC/PNEC ratios for water, sediment, soil and secondary poisoning

	RCR_{STP} PNEC > 2000 µg/l	**RCR Surface water PNEC = 4.4 µg/l**	**RCR Sediment PNEC = 0.43 mg/kg wwt PNEC = 2.0 mg/kg dwt**	**RCR Soil PNEC = 0.28 mg/kg wwt PNEC = 0.31 mg/kg dwt**	**RCRpred/fish PNECfish = 3.33 mg/kg wwt**	**RCRpred/worm PNECworm = 3.33 mg/kg wwt**
Production, formulation and compounding						
Production	< 1.2E-03	0.15	0.83	0.07	0.16	0.01
Compounding Site 1	< 5.3E-03	0.02	0.10	0.30	0.03	0.07
Compounding Site 2 (year 2006)	< 0.4E-03	0.17	0.92	0.03	0.17	0.005
Compounding Site 3	< 1.5E-03	0.002	0.009	0.09	0.003	0.02
Compounding Site 4 (in-house WWTP)	< 0.011	0.006	0.03		0.01	-
Compounding Site 5	< 2.0E-05	0.009	0.05	0.001	0.02	0.0005
Compounding Site 6	0		0.04	-		-
Compounding Site 7 (Large-medium generic)	< 2.5E-03	0.12	0.66	0.14	0.13	0.03
Compounding Site 8 (Small generic)	< 7.0E-04	0.05	0.29	0.06	0.06	0.02
Formulation Large company	< 1.5E-03	0.07	0.40	0.08	0.08	0.02
Formulation Generic scenario	< 2.9E-03	0.13	0.77	0.16	0.15	0.03
Private use						
Southern EU-15	**< 2.4E-03**	**0.11**	**0.61**	**0.20**	**0.12**	**0.04**
measured max. Berlin, Teltow Canal 2003			0.55			
measured 90th percentile Berlin high effluent input area 1996/1997		0.62	(0.95)			
measured 90th percentile Berlin all fish 1996/1997					0.45	

Table 3.4. 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 = 0.44 µg/l		PNEC = 0.086 mg/kg wwt		PNECfish = 3.3 mg/kg wwt	
Production, formulation and compounding						
Compounding Site 7 (Large-medium generic)	0.56	0.11	1.3	0.29	0.05	0.01
Compounding Site 8 (Small generic)	0.23	0.05	0.53	0.05	0.02	0.005
Formulation Large company	0.33	0.07	0.77	0.07	0.03	0.007
Formulation Generic scenario	0.64	0.13	1.5	0.08	0.06	0.01
Private use						
Southern EU-15		**0.11**		**0.30**	**0.01**	**0.004**

Marine compartment

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 3.4. For the private use scenario the marine PEC/PNEC ratios are similar to those in freshwater, All ratios are below 1.

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 HHCB discharge their wastewater into the marine environment only after treatment in a sewage treatment. 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. 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 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. 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 HHCB no data are available from tests that simulate the marine environment in water or sediment. Evidence for rapid degradation is based on various die-away studies in river water resulting in 60% biodegradation of the parent material in 28 days. The overall t½ in river water was 100 hours. 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 3.7 hours. It is concluded that HHCB 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 ranged from 600 to 1600 for the parent compound. There is an indication that HHCB 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 HHCB does not to meet the criterion for bioaccumulation.

The lowest (long-term) experimentally derived NOEC is 0.044 mg/l. Based on the results of 5 GLP studies with no ecologically relevant NOECs below 10 µg/l, HHCB does not does not meet the criterion for environmental toxicity within the scope of the PBT assessment. All

toxicological tests performed on mammals only justify no classification. HHCB 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 HHCB 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 dilution of HHCB, compounding of fragrance oils, formulation of consumer products that contain fragrance oils, and the use of cleaning agents by professional cleaners.

From all activities performed during production and dilution, sampling and diluting constitute the worst case situation. LEV is present in this situation. For estimating inhalation relevant exposure measurement data were not available, therefore exposure is estimated by modelled data. Due to the elevated temperature of the substance adequate personal protection will be used and dermal exposure is considered to be negligible.

For compounding of fragrance oils different worker scenarios are distinguished. The working area is mostly in site in a centrally vented room, therefore LEV is used. The presence of LEV for small size plants is unknown. The results of air monitoring in several plants are used to estimate inhalation exposure. For large and medium sized companies, a separate reasonable worst-case value for 8 hours is made in the risk assessment. For other activities, such as wiping of rinsed vessels, analysis of samples and odour control, inhalation exposure is estimated to be negligible. Dermal exposure during delivery and filling stock tanks is estimated to be negligible because it is assumed that adequate personal protection is used due to the elevated temperature of the substance. For dermal exposure during compounding and wiping of rinsed vessels the results of measured values are used.

During formulation of consumer products it is assumed that the production is highly automated with little or no exposure. Exposure may be possible during handling of the drums and during cleaning and maintenance of the equipment. Because of the very low vapour pressure of the substance after dilution, inhalation exposure is estimated as negligible. Based on the EASE model and observations in practice dermal exposure during cleaning and maintenance is estimated.

Professional cleaners may be exposed to HHCB during handling of the cleaning products. Due to the very low vapour pressure of the diluted substance however, the exposure is assumed to be negligible. For dermal exposure, the exposure level from the use of cleaning agents by professional cleaners is estimated using the EASE model.

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

Table 4.1 Summary table of occupational exposure assessment to HHCB

Workers scenario	Inhalation		Dermal	
	Duration	**Exposure**	**Duration**	**Exposure**
Scenario1 Production and dilution				
- process operator	Short term (3 min/day)	4.5 mg/m^3		Negligible
- blending & dilution	Short term (3 min/day)	4.5 mg/m^3		Negligible
Scenario 2 Compounding of fragrance oils				
- delivery & stocking	Short term (3 min/day; once in 14days)	30 mg/m^3		Negligible
- compounding				
- large and medium size plants	8 h/d	0.013 mg/m^3	2 hours/day	39 mg/day
	Short term (0.25 h/d)	0.1 mg/m^3		
- small size plants	8 h/d	0.065 mg/m^3	2 hours/day	39 mg/day
	Short term (0.25 h/d)	0.1 mg/m^3		
- wiping of rinsed vessels		Negligible	2 hours/day	0,2 mg/day
Scenario 3 formulation				
- handling		Negligible	4 hours/day	1.7 mg/d/420 cm^2
- cleaning & maintenance		Negligible	4 hours/day	0.26 mg/d/1300 cm^2
Scenario 4 professional cleaning				
- handling		Negligible	8 hours/day	0.32 mg/d/ 840 cm^2

4.1.2 Consumer exposure

Consumer exposure occurs from consumer products to which HHCB is added intentionally as a component of the fragrance that enhances the product. It is used as an ingredient in commercial preparations (fragrance oils) intended to be used to fragrance a wide variety of consumer products such as perfumes, creams, toiletries, soaps and shampoos (SCCNFP, 24 October 2000). Two scenarios for direct consumer exposure are discussed: Scenario 1 considers exposure as a result of the use of HHCB in fragrances in cosmetics and Scenario 2 considers exposure via other perfumed household products.

The resulting exposure to HHCB on the skin from the use of a combination of all classes of consumer products on a daily basis was calculated to result in a "worst case situation" of 0.85 mg/kg bw/day (**Table 4.2**). The inhalatory exposure of consumers to HHCB in household cleaning products and air fresheners is lower, in total 0.0085 mg/kg bw/day. These figures are taken forward to the risk characterisation.

Table 4.2. Overview of products and uses that can contain HHCB adapted from the SCCNFP

Type of cosmetic product	Application quantity in grams per application	Application frequency per day	Retention factor (%)(5)	HHCB in product (%)	Exposure to HHCB (mg/day)	Exposure for 60 kg person mg/kg bw/day)
Body lotion	8	0.71	100	0.12	6.83	0.114
Face cream	0.8	2	100	0.090	1.44	0.024
Eau de toilette	0.75	1	100	2.40	18.0	0.30
Fragrance cream	5	0.29	100	1.2	17.4	0.29
Antiperspirant /deodorant	0.5	1	100	0.30	1.5	0.025
Shampoo	8	1	1	0.15	0.120	0.002
Bath products	17	0.29	1	0.60	0.30	0.005
Shower gel	5	1.07	10	0.36	1.93	0.032
Toilet soap	0.8	6	10	0.45	2.16	0.036
Hair spray	5	2	10	0.15	1.5	0.025
				Total	**51.2**	**0.85**

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.

4.1.3 Man exposed indirectly via the environment

The daily human intake resulting from indirect exposure via the environment takes into account exposure to HHCB in food, drinking water and inhaled air. Thus the indirect human exposure is estimated using concentrations in fish, root and leaf crops, meat, milk, drinking water and in air.

It can be concluded that the total human daily intake for the scenarios with the highest environmental concentrations are all in the same order. Man will be mainly exposed via the intake of fish and crops. Using EUSES the highest local human daily intake is estimated for the production scenario and is 2.6 µg/kg bw/day. This value will be taken forward to the risk characterisation. It should be noted that the other scenarios have comparable intake doses as shown in table 4.3. For the regional scenario a value of 0.097 µg/kg bw/day will be taken forward to the risk characterisation.

Table 4.3 Estimated human daily intake of HHCB via environmental routes

	Estimated human daily intake (mg/kg body weight/day)[1]							
Lifecycle step	**Wet fish**	**Root crops**	**Leaf crops**	**Drinking water**	**Meat**	**Milk**	**Air**	**Total**
Private use, SEU scenario	0.0013	0.0011	2.45E-5	3.73E-6	2.5E-6	1.48E-6	4.16E-6	0.0024
Fraction of	0.53	0.46	0.01	0.0016	0.001	0.0006	0.0017	

	Estimated human daily intake (mg/kg body weight/day)[1]							
Lifecycle step	**Wet fish**	**Root crops**	**Leaf crops**	**Drinking water**	**Meat**	**Milk**	**Air**	**Total**
total daily dose								
Production	1.49E-03	3.64E-04	5.74E-04	4.1E-06	5E-05	2.94E-05	9.74E-05	0.0026
Fraction of total daily dose	0.56	0.15	0.22	0.0016	0.019	0.011	0.037	
Compounding large-medium generic	1.04E-03	7.53E-04	1.22E-04	2.9E-06	1.09E-05	6.42E-06	2.08E-05	0.002
Fraction of total daily dose	0.53	0.39	0.06	0.0015	0.006	0.003	0.011	
Formulation generic scenario	1.2E-03	8.76E-04	9.2E-05	3.3E-06	8.3E-06	4.9E-06	1.6E-05	0.0022
Fraction of total daily dose	0.55	0.40	0.04	0.002	0.004	0.002	0.007	
Regional, SEU scenario	9.0E-5	5.6E-6	7.8E-7	2.47E-7	8.1E-8	4.7E-8	1.32E-7	9.7E-5
Fraction of daily dose	0.93	0.06	0.008	0.003	0.0008	0.0005	0.001	

Note 1: 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

HHCB has been detected in human milk samples. The source of HHCB in these samples is not entirely clear. Several publications on HHCB levels in human milk are available Values for risk characterization were chosen from the Sönnichsen study (1999), because this study is well performed by excluding contamination of skin products as much as possible (although possibly not ruled out) highest level of all studies and it involved a fairly large study population (107 volunteers). An analysis of the milk from 107 nursing mothers revealed levels of HHCB with a mean value of 80 µg/kg milk fat and a standard deviation of 149. The minimum and maximum values found were close to zero and 1316 µg/kg milk fat, respectively. A mean and a median fat content of 3.7 and 3.4%, respectively, were also reported. Based on the mean fat content, human milk contains 2.9 µg/kg whole milk (mean) or 48 µg/kg whole milk (highest maximum level),

4.2 EFFECTS

There are no data available on the toxicokinetics of HHCB after oral or inhalation exposure. 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. For inhalation exposure, 100% absorption is taken forward.

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

An *in vitro* dermal absorption study with ^{14}C-ring-labelled HHCB using human epidermal membranes indicated that 5.2% 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 the *in vivo* data indicate a much lower dermal absorption in humans.

The initial plasma elimination half-life in rats and pigs after intravenous administration of ^{14}C-ring-labelled HHCB is approximately 2.1 hr and 1.1 h, respectively but longer half-lives were noted in both species after initial measurements with the pig showing a half-life of approximately 90 hr (48-672 hr after administration). No data on plasma half-life in humans are available for HHCB.

The oral LD_{50} for rats and the dermal LD_{50} for rabbits are both greater than 3000 mg/kg bw. Data for acute inhalation toxicity are not available. The data provided are considered sufficient to meet base set requirements for acute toxicity. There is no need to classify HHCB for acute toxicity.

GLP compliant studies of skin irritation have been performed according to directive 79/831/EEC to groups of either 3 or 4 New Zealand White female rabbits. All tests showed very slight to well-defined erythema and very slight oedema. In only one of the tests did the mean erythema score for Galaxolide 50 DEP exceed 2.0 (the calculated score was 2.1). The solvent in this study, DEP, scored 0.2 for erythema and zero for oedema. The irritating effect was not reversible in 7 out of in total 15 animals in these three studies during an observation period of 7 days, as at that time point still some erythema and/or oedema was seen. Unfortunately, the observation period was not sufficiently long (14 days, according to the test method guideline in Annex V) to evaluate fully the reversibility of the effects. However, the test method guideline also states that the irritation scores should be evaluated in conjunction with the nature and severity of lesions and their reversibility or lack of reversibility. Taking that also into account, the results of the animal studies do not indicate that HHCB is a skin irritant. There is a difficulty though, because according to Annex VI of Directive 67/548, inflammation of the skin is also significant if it persists in at least 2 animals at the end of the observation period [without specifying the length of the observation period and the severity of the effects]. If this guidance is followed strictly, the animal studies would warrant classification as a skin irritant. This issue was discussed at the TC-C&L meeting of November 2005, where it was concluded that it is not warranted to classify HHCB as a skin irritant.

In a Human Repeated Insult Patch Test (HRIPT) for sensitisation, a semi-occlusive patch of 100% neat HHCB showed no irritation after repeated application during the induction phase of the study. Other HRIPTs with diluted HHCB also showed no signs of irritation.

There are some indications from animal studies that HHCB could be a photoirritant. 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 on classification of photoirritating substances are available in Annex VI.

HHCB has been tested for ocular irritation in rabbits in several studies. Some studies used ethanol, a known eye-irritant as solvent, and are not used. In other relevant studies, some ocular irritation was found. However, the effects were not severe enough to require classification according to EU guidelines.

No data on respiratory tract irritation are available.

Although some questionable elicitation reactions have been reported as a result of patch tests in dermatological clinics on sensitive patients, the available data with guinea pigs and humans (Human Repeated Insult Patch Test and maximisation tests) provide no evidence of potential for induction of sensitisation for HHCB. HHCB need not be classified as a skin contact sensitiser.

There is no evidence from studies in experimental animals or with humans, that HHCB is a photosensitiser.

In an adequate 90-day oral study, there were no mortalities or adverse clinical signs. Body weight and food consumption of treated groups were similar to those observed in the control group. No changes in ophthalmologic evaluation were observed and no significant histopathological findings at any dose.

The haematology and blood chemistry differences from controls were all small, often not proportional to dose, often seen only at one time point and/or in one sex, and, with two exceptions, well within historical controls and are not considered to "reduce the capacity of an organism or a component of an organism to function in a normal manner". This, and the fact that these findings were not accompanied by any adverse histopathology or other related findings, leads to the conclusion that they are not adverse effects.

A NOAEL of ≥150 mg/kg bw/day, the highest dose tested, for HHCB in rats is concluded.

Three dermal subchronic studies are available. In two of these there was some evidence of liver weight increases (at 100 mg/kg bw/day for 13 weeks) and body weight decreases (at 36 mg/kg bw/day for 26 weeks) but the magnitude of these effects were not reported and their significance cannot be determined. In a third dermal 26-week study, no effects were seen up to and including the highest dose administered (200 mg/kg bw/day). However, because 1) neither collars nor occlusion were used to prevent oral intake making it impossible to determine actual exposures, 2) the area of application was not reported, and 3) the lack of significance in the findings reported in the first two studies and the lack of an adverse effect dose in the third, it is impossible to conclude a true NOAEL in terms of dermal toxicity.

When administered as part of a fragrance mixture, inhalation exposure to HHCB up to a maximum tested dose of 132 $\mu g/m^3$ for 4 hr per day, 5 days per week for 13 weeks did not result in any toxicity. This study is of limited value because the animals were not exposed to HHCB alone, and HHCB was only present at rather low levels in the mixtures.

HHCB has been tested in a wide array of *in vitro* tests and in an *in vivo* mouse micronucleus test. *In vitro*, HHCB was negative in gene mutation tests with bacteria, in an SOS chromotest with bacteria, in SCE and micronucleus tests with human cells, in an UDS test with primary rat hepatocytes and in a chromosome aberration assay in CHO cells. HHCB also did not induce significant chromosome aberrations in the *in vivo* micronucleus test. Hence, it can be concluded that HHCB is a non-genotoxic substance.

There are no carcinogenicity data available. HHCB is demonstrated to be not genotoxic. There are no indications from repeated dose toxicity studies that could be used to judge carcinogenic potential.

No multigeneration study is available.

In an oral peri/postnatal toxicity study (exposure of only the F_1-generation to HHCB in *utero* during the perinatal phase or through any transfer in the milk of the lactating dams), no toxicity in dams or their F1 and F2 offspring (including behavioural and reproductive capacity

of the F1 animals) was seen at dose levels of 2, 6, or 20 mg HHCB/kg bw per day. 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-HHCB/kg bw per day. HHCB levels up to 2.28 and 32.8 mg HHCB equivalents (including also metabolites)/l of mother's milk, respectively, were reported.

In an oral developmental study there were signs of maternal toxicity at 150 mg/kg bw/day and higher. There was an increased incidence of skeletal malformations and decreased ossification in foetuses at the highest dose of 500 mg/kg bw/day. The NOAEL for maternal toxicity is 50 mg/kg bw/day and for developmental toxicity the NOAEL is 150 mg/kg bw/day. 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 (150 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 studies at doses up to 150 mg/kg bw/day (NOAEL ≥150 mg/kg bw/day).

HHCB has a very weak estrogenic potency *in vitro* but such effects were not seen *in vivo.*

4.3 RISK CHARACTERISATION

4.3.1 Workplace

An overview of the occupational risk characterisation for HHCB is given in **Table 4.1**.

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. Given the highest anticipated short term exposure of 0.03 mg/kg bw (30 mg/m^3 x 0.05 h x 1.25 m^3/h x 1/70 kg^{-1}) and the oral and dermal LD50 values (both >3000 mg/kg bw), it is concluded that there are no indications for concern with respect to acute toxicity by inhalation exposure (**conclusion ii**).

Dermal exposure
Given the dermal LD_{50} in rabbits (>3000 mg/kg bw) and the highest anticipated short term exposure level of 39 mg/d/100 cm^2 (or 39 mg / 70 kg bw = 0.55 mg/kg bw) for scenario 2 (compounding) it is concluded that that HHCB is of no concern for workers with regard to acute dermal toxicity (**conclusion ii**).

Irritation and corrosivity

Skin irritation
- Acute dermal irritation
Based on the available data, HHCB is judged not to be a skin irritant. Hence, there is no concern for workers (**conclusion ii**).

- Photoirritation
In available tests for photoirritation, HHCB was not identified as a photoirritating substance. Therefore, **conclusion ii** may be drawn for this endpoint.

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

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

Eye irritation
HHCB 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
HHCB is not a skin sensitiser (**conclusion ii**).

Photosensitisation
HHCB is not a photosensitiser (**conclusion ii**).

Repeated dose toxicity

Inhalation exposure
The starting point for the risk assessment is the oral NOAEL of ≥150 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 ≥75 mg/kg bw/day. For exposure after inhalation the absorption is assumed to be 100%.

The minimal MOS value is calculated to be 100[2]. Comparing the MOS values (≥2500) with the minimal MOS value, it is concluded that there is no concern for workers with regard to the repeated inhalation exposure for all scenarios (**conclusion ii**).

Dermal exposure
The starting point for the risk assessment is the oral NOAEL of ≥150 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 ≥75 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 5.2% is taken for dermal absorption in all worker scenarios.

The minimal MOS value is calculated to be 100[3]. Comparing the MOS values (≥2600) with the minimal MOS value, it is concluded that there is no concern for workers with regard to the repeated dermal exposure for all scenarios (**conclusion ii**).

Combined exposure
The total internal body burden is determined by uptake after dermal exposure as well as exposure by inhalation of HHCB. This combined exposure should not be applied if a simultaneous exposure can be excluded. Combination of various exposure routes is only relevant for the compounding scenario. The combined total body burden from skin contact and inhalation is 0.0309 mg/kg bw/day. For small size compounders the total may be 0.0383 mg/kg bw/day. The resulting MOS values are ≥2400 and ≥2000, respectively. Based on a comparison with a minimal MOS of 100 (see footnotes 2 and 3), no additional risks are expected for repeated dose toxicity upon combined exposure for all worker scenarios (**conclusion ii**).

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

Mutagenicity

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

Carcinogenicity

There are no data available on the carcinogenic potential of HHCB. The mutagenicity data on HHCB do not indicate a concern with regard to carcinogenicity nor does HHCB 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 ≥150 mg/kg bw/day). Inhalation and dermal developmental studies are lacking.

In an oral developmental toxicity study with rats, developmental toxicity only occurred at maternal toxic dose levels ($NOAEL_{developmental\ toxicity}$ 150 mg/kg bw/day, $NOAEL_{maternal\ toxicity}$ 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. Based on an oral absorption rate of 50% this corresponds to an internal no-effect dose of ≥10 mg/kg bw per day for maternal toxicity.

Given this internal no-effect dose and the highest internal body burden (scenario 2) of 0.0093 mg/kg bw/d for inhalation exposure and 0.029 mg/kg bw/d for dermal exposure, the resulting MOS values are ≥1075 and ≥345 respectively. For combined exposure, a combined internal body burden of 0.0383 mg/kg bw/d results in a MOS of ≥261. 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** (no concern).

4.3.2 Consumers

The starting point for the risk characterisation is the external dermal exposure level of 0.85 mg/kg bw/day together with the inhalatory exposure level of 0.0085 mg/kg bw/day. Because the absorption of HHCB through human skin is 5.2% (worst-case assumption) this external exposure level results in an internal exposure level of 0.044 mg/kg bw/day. For inhalation, 100% absorption is assumed, so the internal exposure level is 0.0085 mg/kg bw/day. The total internal exposure amounts 0.053 mg/kg bw/day.

Irritation

Based on the available data, HHCB is judged not be a skin irritant. Hence, there is no concern for consumers (**conclusion ii)**.

In available tests for photoirritation, HHCB was not identified as a photoirritating substance. Hence, there is no concern for consumers for photoirritation (**conclusion ii)**.

There is no concern for consumers for eye irritation, because HHCB 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

HHCB is not a skin sensitiser in a guinea pig maximization test or in humans in concentrations up to 100%. Consumers are thus not at risk after (repeated) dermal exposure. (**conclusion ii)**.

In available tests for photosensitisation, HHCB was not identified as a photosensitiser. Hence, there is no concern for consumers (**conclusion ii)**.

Repeated dose toxicity

The starting point for the risk assessment is the oral NOAEL of ≥150 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 75 mg/kg bw/day.

Comparing this internal no-effect dose with the calculated human systemic exposure level of 0.053 mg/kg bw/day, a margin of safety (MOS) of ≥1400 can be calculated.

Taking into account intra- and interspecies differences and the use of a NOAEL from a semi-chronic study in which no adverse effects were observed up to and including the highest dose tested, this MOS indicates no concern for consumers following repeated dermal exposure. (**conclusion ii)** based on comparison with a minimal MOS of 200 (factors of 10 for intra- and 10 (4*2.5) for interspecies differences, a factor of 2 for duration extrapolation and a factor of 1 for dose-response).

Mutagenicity

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

Carcinogenicity

There are no data available on the carcinogenic potential of HHCB. The mutagenicity data on HHCB do not indicate a concern with regard to carcinogenicity nor does HHCB possess any structural features that would raise a concern. (**conclusion ii)**

Reproductive toxicity

There are no indications for effects on fertility in the oral 90-day study with rats although in this study investigation was limited to histological examination of the reproductive organs, and no adverse effects were reported up to the highest dose tested (NOAEL ≥150 mg/kg bw/day). Dermal developmental studies are lacking.

In an oral developmental toxicity study with rats, developmental toxicity only occurred at maternal toxic dose levels ($NOAEL_{developmental\ toxicity}$ 150 mg/kg bw/day, $NOAEL_{maternal\ toxicity}$ 50 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 (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 0.053 mg/kg bw/day, a MOS of ≥189 can be calculated. Taking into account intra- and interspecies differences and the lack of effect at the highest dose tested, this MOS indicates no concern for consumers for developmental toxicity (**conclusion ii),** based on comparison with a minimal MOS of 100 (factors of 10 for intra- and 10 (4*2.5) for interspecies differences and a factor of 1 for dose-response).

For consumers, for all relevant endpoints a conclusion ii was reached.

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 HHCB 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 HHCB in mother's milk, a separate risk characterization is necessary for breast-fed babies.

Exposure via food and water

In the EUSES calculations the local total daily intake (external exposure) via fish and root crops is estimated at 2.6 µg/kg bw/day following production, whereas the regional total daily intake is 0.097 µg/kg bw/day.

Repeated dose toxicity

The starting point for the risk assessment is the oral NOAEL of ≥150 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 75 mg/kg bw/day. Taking into account intra- and interspecies differences and the use of a NOAEL from a semi-chronic study in which no adverse effects were observed up to and including the highest dose tested, a minimal MOS of 200 (factors of 10 for intra- and 10 (4*2.5) for interspecies differences, a factor of 2 for duration extrapolation and a factor of 1 for dose-response) is applicable.

A margin of safety (MOS) of >3E+4 can be calculated for the local production scenario. Because the estimated human daily intake doses via food, water and air are comparable for the other local scenarios it can be concluded that HHCB is of negligible risk for man exposed indirectly via the environment (**conclusion ii**). For the regional scale the MOS is even higher (>8E+5), and also a conclusion ii can be drawn.

Mutagenicity

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

Carcinogenicity

There are no data available on the carcinogenic potential of HHCB. The mutagenicity data on HHCB do not indicate a concern with regard to carcinogenicity nor does HHCB possess any structural features that would raise a concern. (**conclusion ii)**

Reproductive toxicity

There are no indications for effects on fertility in the oral 90-day study with rats although in this study investigation for reproductive toxicity was limited to histological examination of the reproductive organs, and no adverse effects were reported up to the highest dose tested (NOAEL ≥150 mg/kg bw/day).

In an oral developmental toxicity study with rats, developmental toxicity only occurred at maternal toxic dose levels ($NOAEL_{developmental\ toxicity}$ 150 mg/kg bw/day, $NOAEL_{maternal\ toxicity}$ 50 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 (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 3846 and 1E+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

Based on the main study human milk contains 2.9 µg/kg whole milk (mean) or 48 µg/kg whole milk (maximum). In an oral peri/post natal study in which female rats were exposed orally to HHCB 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 nor on the pups which were exposed via the milk during nursing. Measurements of levels of HHCB (17.6 and 5.0 µg/ml at 4 or 8 hr post dosing, respectively; parent HHCB 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 1700 to 6000 times the mean levels. This corresponds to approximately 100 to 360 times the maximum level found in human milk samples (2.9 and 48 µg HHCB/kg whole milk, respectively).

Even for the highest concentration 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 3 orders of magnitude between the levels of HHCB 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 HHCB would be the sum of the worst case estimates for the three individual populations, i.e. 0.038 mg/kg bw/day (dermal and inhalation, scenario 2 "compounding" for workers) + 0.053 mg/kg bw/day (dermal and inhalation, consumers) + 0.0026 mg/kg bw/day (oral and inhalation, locally via the environment). This results in a total internal (worst case) combined exposure estimate of 0.094 mg/kg bw/day. The contribution of the exposure via the environment attributes only about 3%. 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 ≥75 mg/kg bw/day from the repeated dose toxicity study, a MOS of 798 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 and a factor of 2 for semichronic to chronic exposure extrapolation, no additional risks are expected for repeated dose toxicity upon combined exposure (**conclusion ii**).

Comparing this value to an internal no-effect dose of ≥10 mg/kg bw per day for maternal toxicity, a MOS of ≥106 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. 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, HHCB is not flammable, not explosive and not oxidising. Therefore, HHCB 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 (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.

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)
Ann.	Annex
AF	assessment factor
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)
d.wt	dry weight / dw
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)
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)

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
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
w	gram weight
GLP	Good Laboratory Practice
h	hour(s)
ha	Hectares / *h*
HPLC	High Pressure Liquid Chromatography
IARC	International Agency for Research on Cancer
C_{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)
kPa	kilo Pascals
K_{oc}	organic carbon adsorption coefficient
K_{ow}	octanol-water partition coefficient
Kp	Solids water partition coefficient
l	litre(s)
log	logarithm to the basis 10
$L(E)C_{50}$	Lethal Concentration, Median
LEV	Local Exhaust Ventilation
m	Meter
µg	microgram(s)

[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.
ISBN 92-827-801[1234]

mg	milligram(s)
MAC	Maximum Accessibility Concentration
MOS	Margins Of Safety
NOAEL	No Observed Adverse Effect Level
NOEC	No Observed Effect Concentration
NOEL	No Observed Effect Level
OEL	Occupational Exposure Limit
OECD	Organisation for Economic Co-operation and Development
OJ	Official Journal
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
pKb	-*logarithm* (to the base 10) of the base dissociation constant
Pa	Pascal unit(s)
PEC	Predicted Environmental Concentration
STP	Sewage Treatment Plant
WWTP	Waste Water Treatment Plant

The report provides the summary of the comprehensive risk assessment of the substance 1,3,4,6,7,8-HEXAHYDRO-4,6,6,7,8,8-HEXAMETHYLCYCLOPENTA-g-2-BENZOPYRAN ((1,3,4,6,7,8-hexahydro-4,6,6,7,8,8-hexamethylin-deno[5,6-c]pyran - HHCB). 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 no concern for any of these populations.