TERTIARY BUTYL HYDROPEROXIDE (TBHP)

CAS-No.: 75-91-2

EINECS-No.: 200-915-7

SUMMARY RISK ASSESSMENT REPORT

Final Report May 2008

The Netherlands

Rapporteur for the risk evaluation of TBHP 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 Organisation 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

The report provides the comprehensive risk assessment of the substance tert-Butyl hydroperoxide (TBHP). 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. For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references, the reader is referred to the original risk assessment report that can be obtained from European Chemicals Bureau[1]. The present summary report should preferably not be used for citation purposes.

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

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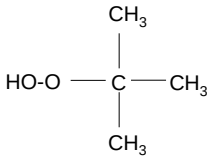
1 GENERAL SUBSTANCE INFORMATION

Identification of the substance

CAS-No.: 75-91-2
EINECS-No.: 200-915-7
IUPAC name: tert-Butyl hydroperoxide
Synonyms: TBHP, 2-Hydroxyperoxy-2-methylpropane, (1,1-)Dimethylethyl hydroperoxide, tert-Butyl hydrogen peroxide,
Trade names: TBHP-70 (T-Hydro), Cadox TBH, Trigonox AW70, Perbutyl H
Molecular formula: $C_4H_{10}O_2$
Structural formula:



Molecular weight: 90.1

Purity/impurities, additives

Purity: 68.4-69.6%
Impurity: 2-Methylpropano-2-ol < 0.5%
Dialkyl peroxide ≤ 0.1%
Ketones ≤ 0.2%
Other hydroperoxides ≤ 1%
Other organics ≤ 0.4%
Additives: Water ≤ 30%

Physico-chemical properties

Table 1.1. Physico-chemical properties of TBHP and TBHP-70

Property	Result	Note
Physical state	liquid (TBHP and TBHP-70)	
Melting point	-8 to –3°C 3 to 5.5°C (crystals)	1
Boiling point	96°C at 760 mm Hg 35 °C at 20 mm Hg (TBHP-pure) 160 °C	1
(Relative) density	Liquid: 935-964 kg/m^3 at 25°C Liquid: 791-902 kg/m^3 at 20°C (TBHP-pure) Vapour: 3.1	1
Vapour pressure	**2700 Pa at 20°C (experimental)** 3070 Pa at 21°C 730 Pa at 25 °C (experimental)	4
Surface tension	56 dynes/cm	
Water solubility	> 100 mg/l at 25 °C and pH 4.3 20,000 mg/l at 20 °C (estimate) ≥ **100,000 mg/l at 22 °C** ca. **100,000** to 150,000 mg/l at 0-50 °C 700,000 mg/l	 5 6
Solubility in other solvents	Soluble in ethanol, ether, chloroform; very soluble in alkali metal hydroxy solution .	
Dissociation constant	12.8 at 20 °C (experimental)	

(pKa)		
Partition coefficient n-octanol/water (log Kow)	**0.7 at 25 °C (experimental)** 0.94 (estimate)	4
Henry's Law constant (H)	**2.43 Pa*m^3/mole (estimate)** 1.63 Pa*m^3/mole at 25 °C (estimate)	7
Atmospheric OH rate Constant	**3E-12 cm^3/molecule*second at 25 °C (experimental)**	1, 8
Flash point	43 °C 62 °C	2
Flammability	Flammable	1
Autoflammability temperature	238 °C	1
Explosive properties	Not explosive Explosive (TBHP-pure)	3
Oxidizing properties	Oxidizing	3
Granulometry	Not applicable (TBHP is liquid)	

1. The same or similar results were found in several literature sources.
2. The hazard of peroxides is not determined by its flammability but by its decomposing properties.
3. Conclusion based on theoretical, and/or structural considerations.
4. Full test report available.
5. Range of concentrations derived from the phase diagram for TBHP-70. The diagram shows one liquid phase up to 100,000-150,000 mg/l (solubility), two liquid phases at ca. 100,000-150,000 mg/l to ca. 650,000 mg/l (above water solubility, but TBHP and water not miscible) and one liquid phase above ca. 650,000 mg/l (TBHP completely miscible with water).
6. Based on composition of TBHP-70 (70% TBHP and 30% water). Concentration is above the water solubility, see above.
7. Henry's Law Constant (H) of 2.43 Pa*m^3/mole: EUSES (version 1.00) calculation, from a vapour pressure (VP) of 2700 Pa and a water solubility (WS) of 100,000 mg/l and the molecular weight (MW) of 90.1 g/mole (H ={[VP*MW]/WS}). These values have been used in the further EUSES calculations underlying the environmental exposure assessment. The Henry's Law Constant of 1.63 Pa*m^3/mole was calculated with the "Henry's Law Constant Program", using the "bond contribution method".
8. The atmospheric OH rate constant of 3E-12 cm^3/molecule*second has been used in the further EUSES calculations underlying the environmental exposure assessment.

Classification and labelling

EU Classification in Annex I: The substance is not yet included in Annex 1, but the indicated Classification and Labelling (as proposed by the rapporteur) has been approved by the EU Commission Working Group on the Classification and Labelling of Dangerous Substances, in April 2006 (environmental effects) and September 2007 (physico-chemical properties and human health effects), respectively.

Classification:

O; R7
R10
Xn; R21/22
T; R23
C; R34
R43
Muta. Cat 3; R68
N; R51/53

Labelling:

Symbols: O, T, N
R- phrases: 7, 10, 21/22, 23, 34, 43, 68, 51/53
S-phrases: 3/7, 14, 26, 36/37/39, 43, 45, 61

Specific concentration limits were concluded with R37 between 5% < C ≤ 10% and R43 above C ≥ 0.1%. This classification and labelling will be included in Annex I of EU 67/548 as tert-butyl hydroperoxide 70% in water because TBHP with less than 30% water is probably explosive.

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

The production of TBHP is located at one site in the Netherlands and at two sites in Germany in the European Union. The total EU production volume is around 14,500 tonnes/year. The total EU processing volume is around 14,200 tonnes/year. Import into and export outside the EU are 143 and 164 tonnes/year, respectively. The difference of about 300 tonnes/year between production volume and processing volume is thought to be caused by the difference in the year of record of the reported amounts. The annual market growth in the European Union is expected to be below 3 percent in the near future as indicated by industry.
The production of TBHP takes place in a closed batch or closed continuous process. The main types of production of TBHP are:

- Direct reaction of isobutane and liquid oxygen.
- Preparation from tertiary-butyl alcohol and 30% hydrogen peroxide in presence of sulphuric acid.
- Oxidising of tertiary-butylmagnesium chloride.
- Epoxidation of propylene catalysed by a molybdenum complex.
- Oxidation of t-butyl alcohol in a 50% hydrogen peroxide solution with a reaction catalyst of silicotungstic acid.

2.2 USE PATTERN

TBHP is primarily used in the chemical industry as starting material (or intermediate) and as a reactive ingredient (catalyst, initiator or curing agent). The quantitative distribution for the processing stage tonnage's is around 20% for IC/UC 3-33 and 80% for IC/UC 11-43, based on the data submitted by industry (table 2.1). Applications are:

- the epoxidation of propylene to propylene oxide (intermediate);
- free radical initiator for polymerisations, copolymerisations, graft polymerisations and curing of polymers (plastic industry);
- free radical initiator to polymerise unsaturated monomers, usually to high polymers. Mainly used by manufacturers of synthetic lattices or water borne dispersions. Also used as a component of catalysts systems for unsaturated polyester resins (resin industry);
- the synthesis of other organic peroxy molecules (as a precursor of initiators) such as perester, persulphate, dialkyl peroxide and perketal derivatives;
- the preparation of speciality chemicals required by fine chemical and performance chemical industries, such as pharmaceuticals and agrochemicals (fungicide).
- the use as an ingredient of hardeners for plastics. These products contain 5 - 20 % TBHP. Hardeners for plastics are also used in the plastic industry.

Table 2.1. Industrial and use categories of TBHP.

Industrial category	**EC no.**	**Use category**	**EC no.**	**Main category**
Chemical industry:	3	Intermediates	33	I b Intermediates stored on site

used in synthesis				
Chemical industry: used in synthesis	3	Oxidising agents	37	III Multi-purpose equipment
Polymers industry	11	Process regulators	43	Type III, "Wet"

3 ENVIRONMENT

3.1 EXPOSURE

3.1.1 General Discussion

The environmental exposure assessment of TBHP will be based on the expected releases of the substance during the life cycle stages: production and processing. TBHP may enter the environment during its production and processing by emission to air and by emission to surface water via effluent from wastewater treatment plants (WWTPs). Furthermore, there may be indirect emission to soil, via deposition from air and/or the use of WWTP sludge on soils.

TBHP, a moderately volatile substance, is readily soluble in water. The results of an evaporation study performed under standard biodegradation aeration conditions show a low volatility from water, while calculations of the (dimensionless) Henry's law constant indicate a moderate volatility from water. The abiotic degradation rate of TBHP is very low, with a half-life (DT50) of 1300 days in ultra-pure water. The biotic degradation rate of TBHP in activated sludge is rapid, with a half-life of 24 minutes; the primary metabolite is tertiary butyl alcohol (TBA). Both the abiotic and biotic degradation rates were found to increase somewhat in the presence of metal-ions (especially Fe^{2+}), but the effect was small. In an activated sludge simulation test, simulating the fate of TBHP in a WWTP, THBP was fully removed from the water and 40% was fully mineralised.

Based on all data, THBP is considered to be readily biodegradable in WWTPs/STPs and a half-life of 24 minutes (elimination rate constant of 1.7/hour) has been used in the exposure assessments as default value for degradation of TBHP in WWTPs/STPs, resulting in 92% removal of THBP in WWTPs/STPs, the remaining 8% in effluent discharged into surface water via the effluent. The elimination rate is based on a 1-h degradation test in unadapted activated sludge. It is noted that the elimination rate constant of 1.7/hour is higher than the maximum TGD default value of 1/hour used for readily biodegradable substances. However, the results of the 1-h tests with unadapted activated sludge show a rapid degradation of TBHP into the primary metabolite TBA and to a limited extent into a further, unidentified metabolite (‘unknown 1’), with around 85% of the amount of TBHP degraded in one hour. In addition, the results of the activated sludge simulation test with adapted sludge indicate that TBHP is fully removed from the water, although not fully mineralised. As in the 1-h test with unadapted activated sludge, the metabolites TBA and ‘unknown 1’ were found in the activated sludge simulation test with adapted sludge. In addition, a third metabolite, ‘unknown 2’, was found in the latter test. The amount of either of the two unidentified metabolites in the effluent was higher than that of the primary metabolite TBA. For the degradation of TBHP entering surface water and soil, TBHP is considered to be inherently biodegradable, thus for these environmental compartments the TGD default values for the half-lives of inherently biodegradable substances have been used in the exposure assessments for water and soil.

TBHP and other hydroperoxides have a relatively weak and polar O-H bond that makes these compounds susceptible to radical reactions as well as to reactions with metal ions and light. In the atmosphere, reactions with (hydroxyl) radicals appear to be most relevant for the abiotic degradation, while in the aquatic environment reactions with metal ions appears to be most relevant. Both the indirect and direct photodegradation of TBHP and other peroxides in air result in the formation of ozone. Thus, TBHP may contribute to the build up of photochemical smog. The contribution of TBHP to this atmospheric effect is considered to be negligible compared to other relevant industrial chemicals (e.g. pentane and toluene) that have the same potential effect, because of much lower emissions of TBHP.

1. Environmental releases

Based on the submitted data the processing in use category "intermediates" (3/33) and use category "process regulators" (11/43) comprises around 20% and 80%, respectively, of the total processing amount. The total EU processing amount of TBHP is assumed to be covered by these two scenarios. Both site-specific and generic scenarios have been used for the exposure assessment of TBHP. Site-specific scenarios are based on actual data from industry on emission patterns etc., whereas generic scenarios are fully based on model calculations for a realistic worst case situation. The total emissions for these sites finally result in one set of local PEC values per site. PEC values in the environmental compartments have been calculated for each production and processing site. The resulting local PEC values are listed in Table 3.1. The continental emissions calculated are largely based on the continental (is total EU) emissions due to processing, i.e. based on the summed emissions due to production at one site. This results in total continental emissions of 165.3 kg/day to air and 511.4 kg/day to waste water. The emissions from industrial sources to waste water and directly to surface water are 485.8 kg/day and 25.6 kg/day, respectively. Around 92% of the amount of TBHP in waste water will be degraded in the WWTP and the remaining 8% will largely end up in the WWTP effluent and thus in surface water. The regional PEC values resulting from the aforementioned total (continental) emissions of 165.3 kg/day to air and 511.4 kg/day to wastewater are presented in Table 3.2.

Table 3.1. Local PEC values in the various environmental compartments for production and processing of TBHP.

	STP (µg/l)	Water (µg/l)	Air (µg/m3)	Soil (mg/kg wwt)
Production Cat. 3/33				
I-a [1]	ng.	2.61E-01	3.57E-2	9.33E-06
I-b [1]	ng.	2.61E-01	3.36E-03	1.05E-06
I-c	7.16E+04	7.19E+01	3.08E+01	1.20+00
Processing Cat. 3/33				
II-a1	See production 1-b			
II-a2	5.02E+02	7.63E-01	1.90E+00	8.81E-03
II-a3	3.01E+03	3.28E+00	1.33E+01	5.33E-02
Processing Cat. 11/43				
II-b1	3.76E+03	3.76E+02	2.28E+00	6.32E-02
II-b2	See production I-c			
II-b3	7.52E+02	7.56E+01	4.60E-01	1.26E-02
II-b4	4.70E+02	4.73E+01	2.62E-02	7.83E-03
II-b5	1.88E+02	1.91E+01	1.29E-02	3.13E-03
II-b6	0.00E+00	2.61E-01	9.17E-03	2.47E-06
II-b7	2.18E+00	2.76E-01	2.70E-01	1.07E-04
II-b8	4.61E+01	4.88E+00	5.55E-03	7.68E-04
II-b9	2.52E+00	5.13E-01	1.09E-02	4.49E-05
II-b10	3.09E+01	2.92E-01	1.86E-02	5.19E-04
II-b11	3.14E+01	3.41E+00	2.24E-02	5.27E-04
II-b12	1.01E+01	1.28E+00	9.50E-03	1.70E-04
II-b13	4.70E-01	3.08E-01	3.65E-03	8.94E-06
II-b14	1.05E+01	1.32E+00	8.71E-03	1.78E-04

II-b15	7.16E+00	2.91E-01	1.10E-02	1.23E-04
II-b16	2.11E+00	2.63E-01	7.19E-03	3.72E-05
II-b17	7.84E-01	3.39E-01	2.24E-02	1.91E-05
II-b18	1.42E+00	2.71E-01	1.90E-01	7.38E-05
II-b19	5.60E+01	5.87E+00	7.19E-02	9.50E-04
II-b20	1.15E+00	2.71E-01	3.01E-02	2.72E-05

ng. negligible

[1] For sites I-a and I-b the submitted data indicate that the TBHP concentrations in the WWTP effluent and the receiving water will be negligible, thus the local PEC in water (2.61E-01) is equal to the regional PEC, see Table 3.2.
At both sites the WWTP sludge is treated as toxic waste, thus it is assumed that the sludge is not applied to the soil. Thus, the PEC soil is solely due to atmospheric deposition.

Table 3.2. Regional PEC values

Compartment	**PEC regional**
PEC air (μg/m^3) (total)	3.36E-03
PEC surface water (μg/l) (total and dissolved)	2.61E-01
PEC sediment (mg/kg_{wwt}) (total)	1.80E-04
PEC agricultural soil (mg/kg_{wwt}) (total)	3.31E-06
PEC natural soil (mg/kg_{wwt}) (total)	1.05E-06

3.2 EFFECTS

3.2.1 Aquatic compartment

The fish tests resulted in 96-h LC50 values of 29 and 57 mg/l for *Pimephales promelas* and *Poecilia reticulata*, respectively. The test with the daphnid *Daphnia magna* resulted in a 48-h EC50 of 14 mg/l (endpoint mobility). The test with the alga *Selenastrum capricornutum* resulted in a 72-h E_rC50 of 1.5 mg/l (endpoint exponential growth rate) and a 72-h E_bC50 of 0.84 mg/l (endpoint biomass); the 72-h NOEC was 0.22 mg/l for both endpoints. The value for algal growth rate (E_rC50 of 1.5 mg/l) and an assessment factor of 1000 have been used for $PNEC_{aquatic}$ derivation, resulting in a $PNEC_{aquatic}$ of 1.5 μg/l (as TBHP).

2. Effects on microorganisms

The toxicity of TBHP-70 to micro-organisms was tested in an activated sludge (respiration inhibition) test, resulting in a 30-minutes EC50 of 17 mg/l (as TBHP). This value has been used for the derivation of the PNEC for STP effluent ($PNEC_{micro\text{-}organisms}$). Applying an assessment factor of 100 results in a $PNEC_{micro\text{-}organisms}$ of 0.17 mg/l (as TBHP).

3. Effects assessment for the sediment

There are no data on sediment-dwelling organisms (benthic organisms), so a PNEC for sediment ($PNEC_{sediment}$) cannot be derived directly from sediment toxicity data. The $PNEC_{sediment}$ and the $PEC_{sediment}$ can be calculated by equilibrium partitioning, but this results in the same PEC/PNEC ratio as for the water compartment. Therefore, no PNEC was derived for sediment.

3.2.2 Atmosphere

There are no data on the effects of atmospheric TBHP on environmental organisms, so a PNEC for air ($PNEC_{air}$) cannot be derived.

3.2.3 Terrestrial compartment

Exposure of tobacco cells to TBHP in a growth solution resulted in concentrations-related effects on both cell growth (decrease of fresh weight) and cell membrane integrity (increase of conductivity in the medium), with in both cases a LOEC of 45 mg/l and a NOEC of 18 mg/l. There are no *in vivo* toxicity data on terrestrial organisms. Therefore the PNEC for the terrestrial compartment was estimated from the $PNEC_{aquatic}$, resulting in a $PNEC_{terrestrial}$ of 0.3 µg/kg wwt (as TBHP).

3.2.4 Non compartment specific effects relevant to the food chain

There are no data on bioaccumulation of TBHP in animals and on biomagnification. Based on an experimental log Kow of 0.7, the bioaccumulation potential of TBHP is considered to be (very) low and food chain effects (secondary poisoning) are not expected. Tertiary butyl alcohol (TBA), the primary metabolite of TBHP, has a log Kow of 0.35. Thus, food chain effects are not expected for TBA either.

3.3 RISK CHARACTERISATION

The risk characterisation ratios (PEC/PNEC) for the environmental compartments on a local and regional scale are shown in table 3.3.

Table 3.3. Risk characterisation for the various environmental compartments.

	PEC/PNEC water	PEC/PNEC WWTP	PEC/PNEC soil
Production			
I-a	0.2	<1	0.033
I-b	0.2	<1	0.004
I-c	**48**	**420**	**4000**
Processing Cat. 3/33			
II-a1	See production I-b		
II-a2	0.5	**3.0**	**29**
II-a3	2.2	**18**	**180**
Processing Cat. 11/43			
II-b1	**250**	**22**	**210**
II-b2	See production I-c		
II-b3	**51**	**4.4**	**42**
II-b4	**32**	**2.8**	**26**
II-b5	**13**	**1.1**	**10**
II-b6	0.2	0	0.008
II-b7	0.2	0.01	0.4
II-b8	**3.3**	0.3	**2.6**
II-b9	0.3	0.02	0.2

II-b10	0.2	0.2	**1.7**
II-b11	**2.3**	0.2	**1.8**
II-b12	0.9	0.06	0.6
II-b13	0.2	0.003	0.03
II-b14	0.9	0.06	0.6
II-b15	0.2	0.04	0.4
II-b16	0.2	0.01	0.1
II-b17	0.2	0.005	0.06
II-b18	0.2	0.008	0.2
II-b19	**3.9**	0.3	**3.2**
II-b20	0.2	0.01	0.1
Regional	0.2		0.004

3.3.1 Aquatic compartment

A PEC/PNEC water of 48 was calculated from the combined production and processing site I-c emission to wastewater (**conclusion iii**). For production sites I-a and I-b, the PEC/PNEC water is <1 **(conclusion ii).** For processing site II-a3 the PEC/PNEC water is 2.2. The scenario is mainly based on default assumptions, but no site-specific data were submitted by industry that could rebut the followed exposure assessment (**conclusion iii**). The PEC/PNEC water for processing site II-a2 is <1 **(conclusion ii).** The PEC/PNEC water for 7 of the processing sites (Category 11/43) is >1. Most PEC/PNEC water values for these sites were calculated with generic scenarios, but no (further) site-specific data were submitted by industry that may rebut the followed exposure assessment (**conclusion iii**). For the remaining processing sites of Category 11/43 the PEC/PNEC water is <1 **(conclusion ii).** The regional PEC/PNEC water, calculated from the regional PEC water (0.26 µg/l) and the $PNEC_{aquatic}$ (1.5 µg/l), is 0.2. Thus, no risk to aquatic organisms is expected at a regional scale **(conclusion ii)**. It is noted that for production/processing site I-c as well as for most of the processing sites with a PEC/PNEC water >1, there is also a PEC/PNEC WWTP >1.
In STPs/WWTPs, TBHP is degraded for around 90%, but not fully mineralised under standard conditions. The primary metabolite tertiary butyl alcohol (TBA) appears to be an inherently biodegradable compound. The aquatic toxicity of TBA is considerably lower than that of TBHP: for micro-organisms a factor of 40, for daphnids a factor of 66, for fish a factor of 120 and for algae a factor of 670, based on short-term tests. Furthermore, algae (which were considerable more sensitive to TBHP than the other taxonomic groups tested) appear not to be specifically sensitive to TBA. Thus, PEC/PNEC values for TBA will be much lower than those currently calculated for TBHP. For all sites, the PEC/PNEC for TBA of water is <1 (**conclusion ii**), with the highest PEC/PNEC value (0.5) for processing site II-b1 and the next highest value (0.1) for production/processing site I-c/II-b2. The results of the activated sludge simulation test show two further metabolites in the effluent, in addition to TBA. These two metabolites, 'unknown 1' and 'unknown 2' have not been identified. It is assumed that, as TBA, these compounds are tertiary compounds that are highly volatile and may be not readily biodegradable. As for TBA, local PEC values for the total amount of the two metabolites ('unknown 1' plus 'unknown 2') can be estimated, but a risk characterisation for these two metabolites is not possible because of the lack of toxicity data. On top of that, because of the (assumed) high volatility these compounds are expected to have a short residence time in water.

3.3.2 Atmosphere

TBHP, as a source of free radicals, may contribute to the build up of photochemical smog. The contribution of TBHP to this atmospheric effect is considered to be negligible in comparison

with other industrial chemicals (e.g. toluene and n-pentane). No risk characterisation is posible for biotic effects.

3.3.3 Terrestrial compartment

The PEC/PNEC soil at production/processing site 1-c and that of 10 of the processing sites is >1. The high PEC/PNEC values of these sites are mainly related to the emissions to waste water. As stated earlier for water and WWTP no data were received that may have reduced these PEC/PNEC ratios to acceptable levels **(conclusion iii)**. The regional PEC/PNEC soil, calculated from the regional PEC Soil (1.05E-06 mg/kg wwt, for natural soil) and the $PNEC_{terrestrial}$ (0.3E-03 mg/kg wwt), is 0.004. Thus, no risk to terrestrial organisms is expected at a regional scale **(conclusion ii)**.

3.3.4 Non compartment specific effects relevant to the food chain

Not relevant.

4 HUMAN HEALTH

4.1 EXPOSURE

4.1.1 Occupational exposure

TBHP is produced and used as a liquid which contains approximately 70 - 80 % TBHP and water. The 70 % aqueous solution has a moderate vapour pressure (3.1 kPa at 21 °C). TBHP is used primarily in the chemical industry as starting material (or intermediate) and as a reactive ingredient (catalyst, initiator or curing agent).

The first scenario includes all activities concerning the production and use of TBHP in the chemical industry. For inhalation exposure measurements were available for different companies and different activities. The reasonable worst case (RWC) exposures are based on measurements for peak activities as well as for full shift. On account of the corrosive effect of TBHP it is assumed that repeated daily contact is avoided by the use of PPE. No measured data were available; therefore dermal exposure (single day contact) estimation was based on modelled data.

The exposure of workers, involved in the formulation and use of hardeners for plastic, is assessed in the second scenario. The measured inhalation exposure levels were considered to be reported with too limited details to be useful for drawing conclusions on RWC levels. Inhalation exposure is based on a combination of model estimates and expert judgement. On account of the corrosive effect of TBHP it is assumed that repeated daily contact is avoided by the use of PPE. No measured data were available; therefore dermal exposure (single day contact) estimation was based on modelled data.

In scenario 3 exposure during the production of products containing <1% TBHP, such as paint, lacquers and varnishes, is estimated. The measured inhalation exposure levels were considered to be reported with too limited details to be useful for drawing conclusions on RWC levels. Inhalation exposure is based on a combination of model estimates and expert judgement. Dermal repeated exposure is in these circumstances possible because products containing less than 10% TBHP are considered as non corrosive. The RWC dermal repeated exposure estimation was based on modelled data.

The use of products containing <1% TBHP is assessed in the fourth scenario. Analogous data were used to estimate inhalation exposure. The combined data from the RIVM fact sheet and the RISKORDERM measurements on styrene were used to estimate the dermal exposure for manual application and cleaning of equipment.

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

Table 4.1 Summary table of occupational exposure assessment to TBHP

Scenario / subscenario	Activity	Frequency (day/year)	Duration (hr/day)	Estimated inhalation exposure level: RWC		Estimated skin exposure level		
				(mg/m^3)	Method	($mg/cm^2/day$)	dose (mg/day)	Method
1: Production and use of TBHP in the chemical industry	peak activities: drumming, sampling, cleaning and maintenance, repair work	100-200	1 – 2	5	measured	0-0.1	42 (single day)	EASE, expert judgement
	Full shift*	100-200	7 – 8	0.5	measured			
2: Production and use of TBHP containing hardeners of plastics	Peak activities: transfer activities, emptying drums, sampling, packaging, cleaning and maintenance, repair work	10-50	1 – 2	10	EASE, expert judgement	0-0.1	42 (single day)	EASE, expert judgement
	full shift*	10-50	7 – 8	3.2	Calculated			
3: Production of products containing <1% TBHP	peak activities: emptying drum and cleaning and maintenance	10-50	0 – 1	10	EASE, expert judgement	0-0.1	42 (single day)	EASE, expert judgement
	full shift**	10-50	6 – 8	3.6	Calculated	0.001-0.01	4	EASE, expert judgement
4: Use of products containing <1% TBHP	Manual application and cleaning of equipment	10 – 50	2 – 4	8	Measured (analogous data)	0.032***	27	EASE, expert judgement
	full shift	10 – 50	7 – 8	4	Measured (analogous data)			

* Full shift exposure calculated from 2 hours at 10 mg/m^3 and an exposure of 0.4 mg/m^3 during the remaining 6 hours.

** Full shift exposure calculated from 0.5 hour at 10 mg/m^3 and an exposure of 4 mg/m^3 during 6 hours and negligible during the rest of the day.

*** Calculated from the dose assuming an exposed surface area of 840 cm^2.

4.1.2 Consumer exposure

TBHP is mainly used in the chemical industry as starting material or as reactive ingredient. As TBHP will be totally converted the exposure of consumers to TBHP as impurities in other products is expected to be absent. The use of TBHP in some consumer products was indicated in several databases but individual consumer products containing TBHP could not be identified. The total amount used in consumer products is low. Also, the two products that were identified but no longer on the market indicate that the concentration is low. An exposure assessment for consumers is therefore not possible.

4.1.3 Man exposed indirectly via the environment

TBHP is completely soluble in water (> 100 g/L), is moderately volatile (2700 Pa) and has a low octanol-water partition coefficient (log K_{ow} of 0.7). In an STP TBHP is degraded for around 90% into the primary metabolite TBA. Based on the low log K_{ow}, the bioaccumulation and sorption potential of TBHP is considered to be very low. The biocentration factor for fish was estimated with the QSAR in EUSES (BCF of 1.41 for fish).

Local exposure

The total daily intakes (EUSES calculations) of TBHP from the production and processing sites are presented in **Table 4.2**.

Table 4.2 Daily doses [mg/kg bw/day] of TBHP through intake of food and air (local scale, all relevant scenarios)

	Total daily intake	Air	Drinking water	Fish	Root crops	Leaf crops	Meat	Milk
Production								
I-a [1]	**7.59E-05**	1.02E-05	6.01E-05	4.88E-06	2.39E-07	5.92E-07	4.18E-10	7.78E-09
I-b [1]	**7.96E-06**	9.55E-07	6.37E-06	5.17E-07	5.55E-08	5.57E-08	4.4E-11	8.21E-10
I-c	**0.292**	8.81E-03	0.237	1.37E-04	0.0453	6.68E-04	1.58E-06	2.95E-05
Processing								
II-a1	**See scenario I-b**							
II-a2	**2.62E-03**	5.45E-04	1.71E-03	9.95E-07	3.27E-04	3.28E-05	1.25E-08	2.33E-07
II-a3	**0.0163**	3.81E-03	0.0103	3.86E-06	1.97E-03	2.28E-04	7.66E-08	1.43E-06
II-b1	**0.0163**	6.54E-04	0.0125	7.17E-04	2.39E-03	4.62E-05	8.38E-08	1.56E-06
II-b2	**See scenario I-c**							
II-b3	**3.26E-03**	1.32E-04	2.5E-03	1.44E-04	4.78E-04	9.28E-06	1.68E-08	3.12E-07
II-b4	**1.87E-03**	7.48E-06	1.56E-03	7.68E-06	2.97E-04	1.45E-06	1.03E-08	1.91E-07
II-b5	**7.49E-04**	3.68E-06	6.22E-04	3.5E-06	1.19E-04	6.21E-07	4.11E-09	7.65E-08
II-b6	**9.74E-06**	2.61E-06	6.37E-06	5.17E-07	8.7E-08	1.52E-07	4.78E-11	8.9E-10
II-b7	**1.01E-04**	7.71E-05	1.56E-05	5.44E-07	2.99E-06	4.49E-06	2.76E-10	5.15E-09
II-b8	**1.93E-04**	1.57E-06	1.53E-04	9.3E-06	2.92E-05	1.91E-07	1.01E-09	1.88E-08
II-b9	**1.83E-05**	3.13E-06	1.23E-05	9.98E-07	1.69E-06	1.88E-07	8.79E-11	1.64E-09
II-b10	**1.29E-04**	5.31E-06	1.03E-04	5.89E-07	1.97E-05	3.76E-07	6.91E-10	1.29E-08

	Total daily intake	Air	Drinking water	Fish	Root crops	Leaf crops	Meat	Milk
II-b11	**1.38E-04**	6.4E-06	1.04E-04	6.49E-06	2E-05	4.4E-07	7.02E-10	1.31E-08
II-b12	**4.56E-05**	2.71E-06	3.38E-05	2.44E-06	6.46E-06	1.79E-07	2.29E-10	4.27E-09
II-b13	**9.45E-06**	1.03E-06	7.4E-06	6.01E-07	3.54E-07	6.12E-08	5.1E-11	9.5E-10
II-b14	**4.68E-05**	2.48E-06	3.53E-05	2.19E-06	6.73E-06	1.67E-07	2.38E-10	4.43E-09
II-b15	**3.28E-05**	3.13E-06	2.43E-05	5.87E-07	4.64E-06	1.98E-07	1.67E-10	3.11E-09
II-b16	**1.15E-05**	2.04E-06	7.39E-06	5.22E-07	1.41E-06	1.24E-07	5.32E-11	9.92E-10
II-b17	**1.63E-05**	6.37E-06	8.2E-06	6.66E-07	6.59E-07	3.73E-07	6.83E-11	1.27E-09
II-b18	**7.07E-05**	5.43E-05	1.07E-05	5.36E-07	2.04E-06	3.16E-06	1.92E-10	3.58E-09
II-b19	**2.58E-04**	2.05E-05	1.87E-04	1.3E-05	3.58E-05	1.32E-06	1.28E-09	2.39E-08
II-b20	**1.71E-05**	8.57E-06	6.61E-06	5.36E-07	9.34E-07	5.01E-07	6.27E-11	1.17E-09

For most scenarios, drinking water and root crops contribute the most to the daily intake via the oral route. It is to be noted that the intake of TBHP via drinking water and food as calculated with EUSES represents the worst case as TBHP is rapidly metabolized in the aquatic compartment into several metabolites, TBA being the most prominent. The contribution of air to the total daily intake is very variable for the different scenarios: it varies from ±0.5% in scenarios II-b4/b5 to 76-77% in scenarios II-b7/b18. In the scenarios with the highest total daily intakes (I-c, II-a3, II-b1 and II-b2) the air contribution is 3, 23, 4 and 3%, respectively.

Regional exposure

On a regional scale, the total daily intake of TBHP is 8.07E-06 mg/kg bw/day. The contribution of air to this total daily intake (12%, based on a regional PEC in air (total) of 3.34E-03 μg/m^3 (EUSES)) is minor as compared to the contribution of food.

4.2 EFFECTS

In the data set only animal studies are available. Most of the studies were not performed according to current standards and were in some cases not suitable to be used in risk assessment.

TBHP is stable in the stomach and intestine and completely absorbed after single and repeated SC and oral exposure at levels between 5 and 50 mg/kg bw. The absorbed TBHP is rapidly converted to 2-methylpropan-2-ol and distributed over the body. The significant reduction of GSH at 2 hours after exposure in liver is consistent with a first-pass metabolism. 2-Methylpropan-2-ol is either excreted in exhaled air, conjugated and eliminated in the urine or oxidised to and excreted in the urine as 2-methyl-1,2-propanediol and 2-hydroxyisobutyric acid. 2-hydroisobutyric acid was the main metabolite in all tissues at 12 hours after treatment. Female rats showed an increased metabolism resulting in lower tissue residues. The results at both dose levels were almost proportional but indicated some saturation of metabolism.

More specific *in vivo* and *in vitro* studies show that besides the major detoxification route TBHP can also form tertiair-butyl peroxyl radicals, tertiair-butoxyl radicals and carbon centered radicals. These radicals can react with many other molecules resulting in many different reaction products.

An oral absorption of 100% was determined for TBHP based on the comparable kinetic parameters after IV and SC exposure for total radioactivity, the high urinary excretion compared to the total recovery and the stability of TBHP in stomach and small intestine contents. However, the bioavailability (presence of substance in the systemic circulation) of TBHP is very low or absent due to the reactivity of TBHP and the rapid conversion to 2-methylpropan-2-ol as shown by the absence of TBHP at 15 minutes after IV injection.

An increase in free radicals in some organs was observed after oral exposure but not after dermal exposure. The increase in free radicals in the liver and blood after oral exposure is considered evidence of a local formation of free radicals. The increase in free radicals in the kidney could be interpreted as an indication of the presence of TBHP in the systemic circulation. However, it is unclear why this increase was not found in the heart or the lung. Overall, the information on the free radical formation are too limited to make a firm conclusion on the bioavailability of TBHP. The absence of systemic bioavailability, as observed in the i.v. study, is confirmed by the pattern of toxicology which showed only local toxicity and no systemic toxicity. Overall, systemic availability of TBHP and radical formation in organs beyond the site of first contact are not expected because of the corrosive properties of TBHP which will prevent such high exposures to occur.

No information on the inhalatory absorption is available. However, given the good absorption after oral exposure indicating good membrane diffusion, the good water solubility and high vapour pressure, 100% absorption after inhalatory exposure is expected and taken forward to the risk characterisation.

Based on the available *in vitro* dermal absorption study and taking into consideration the actual dermal exposure levels used in the risk characterisation, a dermal absorption value of 3.5% is taken forward to the risk characterisation for exposure without occlusion to products containing concentrations below 1% TBHP.

Although not all the studies are according to OECD-guidelines and some are rather dated the data are sufficient to fulfil the Annex VII requirements for acute toxicity. After acute exposure the oral LD_{50} was 406 mg/kg bw 70% TBHP and 560 mg/kg bw 100% TBHP for rats and 800 mg/kg bw (purity not specified) for mice. The dermal LD_{50} was 628 mg/kg bw 70% TBHP for rabbits. With respect to inhalation the LC_{50} was 1850 mg/m³ 100% TBHP for rats and 1292 mg/m³ 100% TBHP for mice. It can be concluded that TBHP is harmful after acute oral and dermal exposure (Xn, R21/22**)**. However, the two inhalatory studies differ with respect to the resulting classification. The study by Thackara and Rhinehart was performed with an aerosol and resulted in an LC_{50} of 1.850 mg/L. However, bearing in mind the vapour pressure of TBHP, it is likely that at least part of the TBHP evaporated and was available as a vapour. The study by Floyd and Stokinger was performed using vapours and resulted in an LC_{50} of 1.8 and 1.3 mg/L for rats and mice, respectively. This indicates classification of 100% TBHP with R23 because it is within the limits of 0.5 to 2 mg/L for a vapour. If the results are converted to concentration for 70% TBHP, than the LC_{50} values in rats are just above 2 mg/l indicating R20 for 70% TBHP but just below 2 mg/l in mice indicating R23 for 70% TBHP. As it is unknown whether humans resemble more to mice or rats in this respect, classification with R23 is proposed for 70% TBHP. Classification with T; R23 and Xn; R21/22 was confirmed by the TC-C&L.

The available data are acceptable to fulfil the Annex VII requirements for irritation testing to the eyes and skin, although it is to be noticed that the skin was exposed for 24 hours. TBHP is corrosive to the skin and causes serious damage to the eyes. Classification with C, R34 (which

covers both effects) is proposed. TBHP also induces respiratory tract irritation, which indicates a classification with Xn, R37. However, R37 is also covered by R34 but is needed at concentrations below 10%. No specific concentration limits are proposed for skin and eye irritation because of the shortcomings and limited details on the studies with lower concentrations. Classification with C; R34 and with Xn; R37 between 5 and 10% was confirmed by the TC-C&L. A concentration of 33 mg/m³ will be taken forward to the risk characterisation for respiratory tract irritation as a LOAEC. (Slightly) increased incidences of lacrimation, red nasal discharge, mucoid nasal discharge and dry rales were observed in the exposed rats.

No information is available on the respiratory tract sensitising potential of TBHP. TBHP is a skin sensitizer in the GPMT. The provided Buehler test is not acceptable due to the low irritation in the induction phase. TBHP is considered a strong sensitizer because 60% of the animals reacted after induction with 0.7% TBHP. This is based on the proposals of the sensitisation expert group. Therefore, classification with R43 and a specific concentration limit of 0.1% is proposed. Classification with R43 and the specific concentration limit of 0.1% were confirmed by the TC-C&L.

The data for oral repeated dose toxicity are sufficient to fulfil the Annex VII requirements. A NOAEL of 30 mg/kg bw/day 70% TBHP (calculated NAEL of 21 mg/kg bw/day for 100% TBHP) from a 45-days gavage study will be taken forward to the risk characterisation. This NOAEL, the highest tested dose for a sufficient period in rats, can be used for systemic and for local effects. Local effects on stomach and/or forestomach were observed at higher doses, i.e. from 50 mg/kg bw/day in range-finding studies to the 45-day study, and from 44 mg/kg bw/day in two limited gavage studies of shorter duration in rats and mice. In the latter study with mice, also reductions in body weight were observed at 44 mg/kg bw/day and higher.

After dermal exposure of rats and mice for approximately 14 days only local effects were found at doses up to 350 mg/kg bw/day. A NOAEL of 44 mg/kg bw/day for local effects was derived from these studies. This NOAEL can be taken forward to the risk characterisation as a NOAEL for local effects but not as a NOAEL for systemic effects due to the limitations of the studies such as the low number of parameters studied. This NOAEL corresponds with a NOAEC of 2.2%.

For inhalation repeated dose toxicity no (useful) data were available.

Based on the positive effects in the bacteriological gene mutation tests, a positive result in a $TK^{+/-}$ assay with mammalian cells, and the fact that TBHP induces chromosomal aberrations and aneuploidy it is concluded that TBHP is mutagenic *in vitro*. Moreover, the fact that TBHP induces DNA base damage and DNA fragmentation indicates that TBHP is intrinsic genotoxic *in vitro.*

The data set on genotoxicity of TBHP *in vivo* towards somatic cells is limited. Therefore it is difficult to reach a conclusion on the genotoxicity *in vivo* of TBHP. The available *in vivo* studies indicate that TBHP induces DNA adducts in the liver and stomach after oral exposure to a dose exceeding the oral LD50. Since lower dose levels were not tested it is impossible to make a statement on this effect at lower levels. Therefore, the worst case assumption is made that mutagenicity will occur at all dose levels including the levels to which humans are exposed.
The available *in vivo* data show that TBHP does not induce chromosomal aberrations in bone marrow *in vivo*. A limited Comet assay in rat liver after subcutaneous exposure was negative. TBHP was negative in several tests on the bone marrow.

TBHP induces dominant and recessive lethal mutations in Drosophila when eggs are exposed or adults are injected, but no mutagenic activity is detected in adults upon oral exposure or exposure by inhalation. TBHP is positive in a dominant lethal assay in mice after intraperitoneal exposure and induces changes in sperm morphology. Comparable effects on fertility were found in additional tests on rats and mice after intraperitoneal exposure. This could be a local effect of TBHP on the testis because substances can travel from the abdominal cavity through the inguinal channel to the testis.

The ADME study shows that TBHP is rapidly converted *in vivo* to 2-methylpropan-2-ol. After intravenous injection, no TBHP but mainly 2-methylpropan-2-ol was found in blood at the earliest measurement of 15 minutes after injection. Also after subcutaneous injection, no TBHP but mainly 2-methylpropan-2-ol was found in blood and tissues at the earliest measurement of 2 hours after injection. Based on the rapid conversion of TBHP to 2-methylpropan-2-ol after parenteral administration, no detectable levels of TBHP will also be expected after oral, dermal and inhalatory exposure due to the slower absorption and the first pass effect in the liver after oral exposure. 2-Methylpropan-2-ol was tested for mutagenicity by the NTP in 1995 and all *in vitro* and *in vivo* results were negative.
As mentioned above, TBHP is clearly genotoxic and mutagenic *in vitro* and probably genotoxic *in vivo*. TBHP was negative in several mutagenicity tests on the bone marrow. However, seen the rapid conversion of TBHP to the non-mutagenic compound 2-methylpropan-2-ol, it is very likely that TBHP did not reach the bone marrow. TBHP is mutagenic in germ cells after *in vivo* exposure (changes in sperm morphology and an increase in dominant lethal mutations) but this was only seen after intraperitoneal exposure. However, it is unlikely that TBHP will reach the gonads through relevant routes of exposure in view of the rapid conversion to 2-methylpropan-2-ol. Therefore, the positive results of these germ cell tests are considered evidence for a local mutagenic effect. Consequently, the *in vivo* mutagenicity of TBHP through relevant routes is likely confined to somatic cells in the tissues of first contact and could possibly result in local carcinogenicity. The formal conclusion is that TBHP is mutagenic. However, as TBHP will not reach the germ cells after oral, inhalation and dermal exposure, exposure to TBHP is unlikely to result in inheritable genetic damage.

The mutagenic effects of TBHP are probably due to the formation of TBHP-derived radicals after one-electron oxidation or one-electron reduction and their reaction with DNA. This mechanism would theoretically lead to no threshold for the mutagenicity. However, radical formation and their reaction with DNA will probably depend on the antioxidant levels of the cell with an increase in DNA adducts at TBHP levels which induce a reduction in the antioxidant levels. This would indicate a sub-linear dose-effect relation but could also indicate a threshold. No information is available on the dose-effect relation within the sites of first contact. The available studies on the testis after intraperitoneal exposure indicate that DNA effects were found at or around TBHP levels which also reduce the antioxidant level but at levels without histological changes. However, an increase in ROS and the activity of enzymatic antioxidants (which can be seen as secondary to the increase in ROS) was found at levels without a decrease in non-enzymatic antioxidants like GHS. The limited studies on the testis do not provide sufficient evidence that the formation of free radicals and possible DNA effects including mutations cannot occur at levels without a reduction in non-enzymatic antioxidants, nor do the in vivo metabolism data exclude the occurrence of radical formation before glutathione is depleted. Further, no information is available on the extrapolation to other tissues including the sites of first contact. Based on the available data it is assumed that TBHP is a non-threshold mutagen.

Classification with Muta. Cat.2; R46 is not justified because TBHP does not reach the gonads after oral, inhalation and dermal exposure. However, classification with Muta. Cat. 3; R68 is proposed because it is assumed that TBHP will be mutagenic at the sites of first contact in somatic cells. Classification with Muta. Cat. 3; R68 was confirmed by the TC-C&L.

No inhalatory and oral carcinogenicity studies with TBHP are available. TBHP is, however, rapidly converted to 2-methylpropan-2-ol and for this compound oral carcinogenicity studies are available. These studies show very small increases in systemic tumours. However, these dose levels of 2-methylpropan-2-ol can not be reached by treatment with TBHP because these levels are above the LD50 of TBHP for mice, and above the dose level of TBHP inducing local effects to the stomach in rats. From these observations it is concluded that chronic exposure to TBHP will most probably not result in 2-methylpropan-2-ol levels that can induce systemic tumours.

It is assumed that TBHP will be mutagenic at the sites of first contact in somatic cells. However, based on the rapid conversion of TBHP, it is unlikely that TBHP can reach the systemic circulation through normal routes of exposure. Consequently, carcinogenicity limited to tissues that are exposed to the parent TBHP (i.e. tissues of first contact) cannot be excluded.

Useful data on the potential local carcinogenic effects of TBHP are not available, unfortunately. In a single very limited dermal study one clearly toxic concentration of TBHP was capable of promoting the development of dermal tumors after induction by 4-nitroquinoline 1-oxide. Therefore information on the local carcinogenicity is needed. This information could be derived either by read-across from other substances in case the read-across is sufficiently validated and based on sufficient data or based on tests. This should ideally be through the oral, dermal and inhalatory route because it is unknown whether and how local carcinogenicity can be extrapolated from one route to the other. However, from a practical point of view it is proposed to start with one route and the need for additional routes will depend on the results. Information on the carcinogenicity by the inhalatory route is preferred because this route is relevant for both workers and humans exposed via the environment.

The NTP had nominated TBHP for carcinogenicity testing, apparently for the dermal route. Fourteen-day oral and dermal range finding studies have meanwhile been performed. The NIEHS recommended in 2006 after the range-finding studies that no further studies should be done with TBHP because of the minimal exposure to TBHP, the negative result in a dermal carcinogenicity study and the results of a number of other organic peroxides in a short-term initiation and/or promotion protocol. The argument for not testing, that exposure is minimal, is not consistent with the current exposure estimates as specified in section 4.1. In addition, the dermal carcinogenicity study is assessed as inadequate in the RAR. The results of the initiation / promotion study indicate that several organic peroxides are negative in this screening model. However, seen the limitations of this model it is difficult to extrapolate this result. References in this study show the presence of more extensive carcinogenicity studies with some organic peroxides. However, a full study on all available carcinogenicity data on organic peroxides and the justification of the read-across approach is not available.
In conclusion, the available data are insufficient to determine whether TBHP may be carcinogenic at the sites of first contact. Besides, it is to be noted that no information is available on whether dermal carcinogenicity data can be extrapolated to the sites of first contact after inhalation and oral exposure.

In an oral screening study no toxicological relevant effects on fertility, reproductive performance, and development were seen up to 30 mg/kg bw/day 70% TBHP, the highest dose

tested. TBHP is rapidly converted to 2-methylpropan-2-ol. Therefore only 2-methylpropan-2-ol will be available to the reproductive organs. Chronic exposure to 2-methylpropan-2-ol up to levels of 420 mg/kg bw/day or higher in rats and mice did not induce effects on the reproductive organs. This confirms the absence of effects on fertility in the oral screening study.
In a developmental toxicity study a dose of 50 mg/kg bw/day 70% TBHP, the highest dose tested, did not result in developmental toxicity. It is recognised that these negative results do not exclude the potential for reproductive and developmental effects at higher doses than tested. However, considering these negative test results on relevant parameters and given the effects seen in the range-finding studies (especially submucosal oedema in the stomach wall, in males at 50 mg/kg bw and higher and in females at 107 mg/kg bw and higher) and in the repeated dose toxicity study (effects in males at much lower levels in organs other than reproductive organs), further testing at higher dose levels is not expected to provide relevant additional information.
With regard to the significant increase in post-natal pup mortality at 30 mg/kg bw/day in the oral screening study, this observation is not considered a treatment related effect. This is supported by the studies with 2-methylpropan-2-ol where increased post-natal mortality was only seen at much higher dose levels (lower doses not tested) in rats and not in mice at much higher dose levels.
The available data on 2-methylpropan-2-ol indicate reproductive effects at much higher dose levels (6000 mg 2-methylpropan-2-ol/m^3) than can achieved by exposure to TBHP (LC_{50}: 1850 mg/m^3). Therefore, these effects are unlikely to be found after exposure to TBHP.

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.

In the scope of the assessment of existing substances, dermal exposure to corrosive concentrations is not assessed. For the handling of corrosive substances and formulations, it is assumed that daily dermal exposure can be neglected because workers are protected from dermal exposure and immediate dermal contacts occur only accidentally. Techniques and equipment (including PPE) are used that provide a high level of protection from direct dermal contact. Eye protection is obligatory for activities where direct handling of TBHP occurs.
However, dermal exposure to dilutions of TBHP, that result in a substance or formulation which has no corrosive labelling (dilutions containing <10% TBHP, according to EU classification and labelling commission), also occurs. Dermal exposure to such non-corrosive dilutions of TBHP (in scenario 3 (Production of products containing <1% TBHP – general mixing and packaging of products') and scenario 4 (Use of products containing <1% THBP)) cannot be neglected and will be taken into account.
Furthermore, acute and repeated inhalation exposure to TBHP will be considered.

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.

Acute toxicity

Inhalation exposure

The mouse and rat LC_{50} values, 1292 mg/m^3 and 1845 mg/m^3 (100% TBHP), respectively show that mice are more sensitive to TBHP. Starting-point for the risk assessment of acute inhalation toxicity is the 4-hour LC_{50} value of 1292 mg/m^3 for mice. Adapting this starting point by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers conducting light activity compared to being in rest, results in an adapted level of 866 mg/m^3. The minimal MOS value is calculated to be >>12.5[2]. As an LC_{50} is used as starting point for the risk characterisation, a factor of <10 as margin between the MOS and the established part of the minimal MOS is not considered acceptable.

Comparing the MOS value of scenario 1 (>173) with the established part of the minimal MOS (>>12.5), it is reasonably not expected that this will result in a concern for workers (**conclusion ii**).

Comparing the MOS values of scenarios 2, 3 and 4 with the established part of the minimal MOS of >>12.5, it is concluded that the margin between the MOS and the established part of the minimal MOS is lower than 10. It should be noted that MOS for acute inhalation toxicity is based on a 4-hour LC_{50} while the actual human exposure concerns only 1-2 hr in some scenarios. Applying Haber's Law results in MOS values of 109, 137.5 and 108 for scenarios 2, 3 and 4, respectively which allows an additional uncertainty factor of >10 next to the already established part of the minimal MOS with regard to scenario 3 (**conclusion ii**). However, acute toxic effects due to acute inhalation exposure cannot be excluded for scenarios 2 and 4 (**conclusion iii**).

Dermal exposure

Only one acute dermal toxicity study with rabbits was available. The LD_{50} of 628 mg/kg bw is used as a starting point for acute dermal toxicity. Based on this value for a 70% TBHP dilution, a LD_{50} of 440 mg/kg bw is calculated for 100% TBHP.

In scenario 1 and 2, dermal exposure is considered to occur only accidentally, so **conclusion ii** is justifiable.

The minimal MOS value is calculated to be >>30[3]. The MOS values between the LD_{50} value and the estimated external dermal doses are calculated to be 7333, 733 (both scenario 3) and 314 (scenario 4). Furthermore, the following aspects should be emphasised:

- at the dose levels tested in the acute dermal toxicity study local dermal effects were observed which may have resulted in a higher absorption of TBHP in the rabbits;
- the MOS for acute dermal toxicity is based on a 24-hour LD_{50} while the exposure duration for the various workers scenarios concern 1-6 hours, which may indicate an underestimation of the MOS value.

Therefore, comparing the MOS values with the established part of the minimal MOS and taking into account the above described aspects, it is reasonably not expected that this will result in a concern for workers (**conclusion ii**).

Irritation

Acute irritation

TBHP is considered to be a corrosive agent (concentrations ≥10%). Dermal exposure to corrosive concentrations of TBHP is considered to occur only accidentally if the required

[2] Minimal MOS inhalation acute toxicity (>>12.5) = 2.5 (interspecies) x 5 (intraspecies) x >>1 (dose response / type of critical effect)

[3] Minimal MOS dermal acute toxicity (>>30) = 2.4*2.5 (interspecies) x 5 (intraspecies) x >>1 (dose response / type of critical effect)

protection is strictly adhered to. Therefore, **conclusion ii** is justifiable for scenarios in which corrosive concentrations of TBHP are handled.

Dermal exposure to irritating, but non-corrosive, dilutions of TBHP (concentrations <10%) also occurs. The data available do not permit a quantitative risk characterisation. However, it is assumed that existing controls (i.e., engineering controls and personal protective equipment based on classification and labelling with R38) are applied for these exposure situations. Therefore, in the case that engineering controls and personal protective equipment are effectively used, it is concluded that TBHP is of no concern for workers with regard to skin irritation for scenarios in which non-corrosive concentrations are handled (**conclusion ii**).

Eye
Given the results of the eye irritation studies, it is concluded that TBHP is of concern for workers with regard to local effects on the eye. However, ocular exposure can be excluded as effective use of personal protective equipment (for the eyes) is assumed. Therefore, in the case that engineering controls and personal protective equipment are effectively used, it is concluded that the substance is of no concern for workers with regard to eye irritation (**conclusion ii**).

Respiratory tract irritation
TBHP caused increased incidences of lacrimation, red nasal discharge, mucoid nasal discharge and dry rales from a concentration of 33 mg/m³ (slightly) in rats. Comparison of the concentration of 33 mg/m³ (LOAEC) with the estimated short-term exposure levels results in MOS values of ≤6.6 for all scenarios. The minimal MOS is calculated to be 37.5[4]. Therefore, local effects of the respiratory tract cannot be excluded for all scenarios (**conclusion iii**).

Sensitisation
Skin
Based on the results of the GMPT study, it is concluded that TBHP is a skin sensitiser. The data are insufficient for a quantitative risk characterisation. However, as sensitisation is considered as a non-threshold effect and as dermal exposure may occur in different scenarios, it is concluded that TBHP is of concern for workers (**conclusion iii**).

Respiratory tract
No information is available on the respiratory tract sensitising potential of TBHP.

Repeated dose toxicity
Inhalation exposure
Local effects
There is no data available on respiratory irritation following repeated inhalation exposure.

Systemic effects
Starting points for the risk characterisation are the NOAEL of 30 mg/kg bw/day from the 45-day oral gavage study with rats with 70% TBHP (calculated NAEL of 21 mg/kg bw/day for 100% TBHP) and the assumption of 100% oral absorption and 100% respiratory retention.
Given the estimated frequency of exposure (100-200 d/year for the chemical industry and 10-50 d/year for all other scenarios) chronic and semichronic exposure is assumed, respectively, for

[4] Minimal MOS inhalation acute toxicity (37.5) = 2.5 (interspecies) x 5 (intraspecies) x 3 (dose response / type of critical effect)

risk characterisation. The minimal MOS[5] is calculated to be 100 for chronic exposure and 50 for semichronic exposure.
Given the MOS value for inhalation exposure for scenario 1 (294), there is no concern for this scenario (**conclusion ii**).
The MOS values for the scenarios 2 (46), 3 (41) and 4 (37) are slightly lower than the minimal MOS (50). Considering the relative small difference between the minimal MOS and the MOS and taking into account the uncertainties and worst case approaches taken in both exposure assessment and derivation of the minimal MOS, **conclusion ii** is considered acceptable for these scenarios.
The MOS value of 18 for the scenario 4 regarding 'Use of products containing <1% TBHP - Manual application and cleaning of equipment' is considered too low compared to the minimal MOS value of 50. Therefore, a **conclusion iii** is applicable for this scenario.

Dermal exposure
Local effects
Dermal exposure to corrosive concentrations of TBHP is considered to occur only accidentally if the required protection is strictly adhered to. Therefore, **conclusion ii** is justifiable for scenarios in which corrosive concentrations of TBHP are handled (scenario 1 and 2).
With regard to the available repeated dermal dose studies, a NOAEC of 2.2% TBHP (in 50 percent aqueous acetone) for local effects was derived in mice. In scenario 3 and scenario 4, workers may be exposed to TBHP concentrations lower than 1%. Comparing this TBHP exposure concentration with the NOAEC of 2.2%, it is concluded that TBHP is of no concern for workers with regard to local dermal effects (**conclusion ii**).

Systemic effects
Starting points for the risk characterisation are the NOAEL of 30 mg/kg bw/day from the 45-day oral gavage study with rats with 70% TBHP (calculated NAEL of 21 mg/kg bw/day for 100% TBHP) and the assumption of 100% oral absorption and 3.5% dermal absorption. Although TBHP is a corrosive substance route-to-route extrapolation is considered applicable for systemic effects.
Given the estimated frequency of exposure (10-50 d/year for all other scenarios) semi-chronic exposure is assumed. The minimal MOS is calculated to be 50[6].
In scenarios 1 and 2, dermal exposure is considered to occur only accidentally, so **conclusion ii** is justifiable.
Based on a comparison of the MOS values for scenario 3 and 4 (≥1560) with the minimal MOS value, it is concluded that there is no concern for workers with regard to systemic effects due to repeated dermal exposure to TBHP (**conclusion ii**).

Combined exposure
Systemic effects
The internal body burden due to inhalation and dermal exposure is mainly determined by inhalation exposure and therefore for combined exposure the same conclusions as for inhalation exposure are applicable.

<u>Mutagenicity</u>

[5] Minimal MOS inhalation chronic repeated dose toxicity (100) = 4*2.5 (interspecies) x 5 (intraspecies) x 2 (semichronic to chronic extrapolation)
Minimal MOS inhalation semichronic repeated dose toxicity (50) = 4*2.5 (interspecies) x 5 (intraspecies)
[6] Minimal MOS dermal semichronic repeated dose toxicity (50) = 4*2.5 (interspecies) x 5 (intraspecies)

Based on the available data, it is concluded that TBHP is considered genotoxic *in vivo* at sites of first contact. This conclusion is based on the worst case assumption that there is no threshold for this effect. Therefore, **conclusion iii** is reached.

Carcinogenicity
TBHP is considered to be mutagenic at the sites of first contact in somatic cells. However, based on the rapid conversion of TBHP, it is unlikely that TBHP can reach the systemic circulation through normal routes of exposure. Consequently, carcinogenicity limited to tissues that are exposed to the parent TBHP (i.e. tissues of first contact) cannot be excluded. Useful data on the potential local carcinogenic effects of TBHP are not available, unfortunately. Therefore information on the local carcinogenicity is needed (**conclusion i**).

Toxicity for reproduction
Fertility
No specific effects on fertility were observed in an oral Combined Repeated Dose and Reproductive/Developmental Toxicity Screening Study in rats. Therefore, no quantitative risk characterisation is performed and there is no reason for concern (**conclusion ii**).

Developmental toxicity
No specific teratogenic potential and/or impairment of embryo/fetal development were observed in an oral embryotoxicity/teratogenicity study in rats. Therefore, no quantitative risk characterisation is performed and there is no reason for concern (**conclusion ii**).

4.3.2 Consumers

TBHP is mainly used in the chemical industry as starting material or as reactive ingredient. As TBHP will be totally converted the exposure of consumers to TBHP as impurities in other products is expected to be absent. The use of TBHP in some consumer products was indicated in several databases but individual consumer products containing TBHP could not be identified. A risk characterisation for consumers is therefore not possible. The total amount used in consumer products is low. Also, the two products that were identified but no longer on the market indicate that the concentration is low. Therefore, no risk characterisation is performed.

4.3.3 Man indirectly exposed via the environment

Only oral and inhalatory exposure is taken into account for exposure via the environment as exposure is via air and via food and water. Further, the exposure duration is considered to be chronic as exposure via the environment is a continuous process. Exposure estimates were provided in table 4.1.

Repeated dose toxicity
Starting point for the risk characterisation for humans exposed via the environment is the NOAEL of 30 mg/kg bw/day from the 45 day oral gavage study in rats with 70% TBHP. From the oral NOAEL, a NAEL of 21 mg/kg bw/day is calculated for 100% TBHP. Applying a minimal MOS of 200 to the NAEL of 21 mg/kg bw/day implies that only scenarios with a total daily intake above 0.105 mg/kg bw are of concern. This is only the case for the local sites I-c and II-b2, both with an estimated total daily intake of 0.292 mg/kg bw, mainly (97%) coming from food and water. Hence, for these two local sites a **conclusion iii** is reached. For all other local

sites (with 0.0163 mg/kg bw as the highest total daily intake), as well as for the regional scenario (total daily intake of 8.07E-06 mg/kg bw), a **conclusion ii** can be drawn.

Mutagenicity
Based on the available data, it is concluded that TBHP is considered genotoxic *in vivo* at sites of first contact. This conclusion is based on the worst case assumption that there is no threshold for this effect. Therefore, **conclusion iii** is reached for all local sites and for the regional scenario.

Carcinogenicity
TBHP is considered to be mutagenic at the sites of first contact in somatic cells. However, based on the rapid conversion of TBHP, it is unlikely that TBHP can reach the systemic circulation through normal routes of exposure. Consequently, carcinogenicity limited to tissues that are exposed to the parent TBHP (i.e. tissues of first contact) cannot be excluded. Useful data on the potential local carcinogenic effects of TBHP are not available, unfortunately. Therefore information on the local carcinogenicity is needed (**conclusion i**).

Fertility
No quantitative risk characterisation is performed as no adverse effects regarding this endpoint were observed up to dose levels causing other toxic effects (see repeated dose toxicity). Therefore, **conclusion ii** is applicable.

Developmental toxicity
No quantitative risk characterisation is performed as no adverse effects regarding this endpoint were observed up to dose levels causing other toxic effects (see repeated dose toxicity). Therefore, **conclusion ii** is applicable.

The risk characterization for man indirectly exposed via the environment resulted for all local sites and for the regional scenario in a conclusion iii for the endpoint mutagenicity, a conclusion i for carcinogenicity and a conclusion ii for reproductive toxicity. For repeated dose toxicity the conclusions depend on the scenario. A conclusion iii was reached for the local sites I-c and II-b2, while for all other local sites and for the regional scenario a conclusion ii was reached.

4.3.4 Combined exposure

As there is no consumer exposure, combined exposure concerns only the combination of worker exposure and exposure of man via the environment. However, for workers a **conclusion i** or a conclusion iii is reached for all endpoints that are also of concern for man exposed via the environment. The additional exposure via the environment will not change these conclusions. Therefore, no combined exposure assessment and risk characterization was performed.

4.3.5 Physico-chemical properties

TBHP is flammable and oxidizing and is labelled with respect to these physico-chemical properties. However, it is assumed that existing controls (i.e., engineering controls and personal protective equipment based on classification and labelling with R7 and R10) are applied for exposure situations. Therefore, in the case that engineering controls and personal protective equipment are effectively used, it is concluded that TBHP is of no concern with regard to

physico-chemical properties (**conclusion ii**). There is no need for further information and/or testing.

5 OVERALL RESULTS OF THE RISK ASSESSMENT

5.1 ENVIRONMENT

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

This conclusion is reached, because the local PEC/PNEC is >1 for the aquatic environment (including WWTP) and/or terrestrial environment for one production site and a number of processing sites. Although the exposure assessment is based on a number of default assumptions, no additional data were submitted by industry that may rebut the currently followed approach for the PEC calculations.
It is stressed that from a scientific perspective, a conclusion (**i**) would have been more appropriate, as refinement of both PEC values (now based on a number of default assumptions instead of site-specific data) and the PNEC values (now based on very limited data) may be possible. However, Industry has not supported to provide additional exposure data or to conduct additional ecotoxicological studies and thereby implicitly accepted a conclusion (**iii**) for a number of sites. Furthermore, it can be questioned if all PEC/PNEC values would be lowered sufficiently by a refinement of PEC and PNEC values, as some of the current PEC/PNEC values are far above 1.

5.2 HUMAN HEALTH

Workers

Conclusion (i) There is a need for further information and/or testing.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (i) is reached because:
local carcinogenicity can not be excluded as TBHP is considered mutagenic to the sites of first contact and useful data on the potential local carcinogenic effects of TBHP are not available. This conclusion applies to all scenarios.

Conclusion (iii) is reached because:
- systemic effects cannot be excluded after acute inhalation exposure in the scenarios 'Production and use of TBHP containing hardeners of plastics' and 'Use of products containing <1% TBHP';
- respiratory tract irritation cannot be excluded after inhalation exposure in all scenarios;
- skin sensitisation cannot be excluded after dermal exposure in all scenarios;
- systemic effects cannot be excluded after repeated inhalation exposure in the scenario 'Use of products containing <1% TBHP - Manual application and cleaning of equipment'; and
- mutagenic effects after dermal and inhalation exposure cannot be excluded in all scenarios.

It might be possible that in some workplaces adequate worker protection measures are already being applied.

Consumers

Not applicable because there is no consumer exposure.

Humans exposed via the environment

Conclusion (i) There is a need for further information and/or testing.
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.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (i) is reached because:
local carcinogenicity can not be excluded as TBHP is considered mutagenic to the sites of first contact and useful data on the potential local carcinogenic effects of TBHP are not available. This applies to all local sites and for the regional scenario.

Conclusion (ii) applies to the endpoint reproductive toxicity for all local sites and for the regional scenario, and to the endpoint repeated dose toxicity for the sites not mentioned below.

Conclusion (iii) applies to the endpoint mutagenicity for all local sites and for the regional scenario, and to the endpoint repeated dose toxicity for the local sites I-c and II-b2.

Combined exposure

A risk characterisation for combined exposure was not performed because the conclusions already made for each scenario will not be changed by adding the exposure via the environment.

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[7]
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)

[7] 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