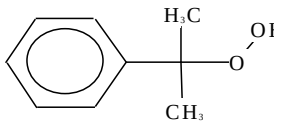
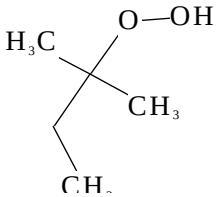
SIDS INITIAL ASSESSMENT PROFILE

CAS Nos.	80-15-9 3425-61-4
Chemical Names	hydroperoxide, 1-methyl-1-phenylethyl (CHP) hydroperoxide, 1,1-dimethylpropyl (TAHP)
Structural Formulae	 CHP  TAHP

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

1-Methyl-1-phenylethylhydroperoxide (cumene hydroperoxide; CHP, CAS No. 80-15-9) and 1,1-dimethylpropylhydroperoxide, (*tert*-amyl hydroperoxide; TAHP, CAS No. 3425-61-4) are monosubstituted derivatives of hydrogen peroxide with the general molecular formula ROOH. These compounds are further classified together as tertiary hydroperoxides as they share the general molecular formula R-C(CH_3)$_2$-O-OH. TAHP is a low molecular weight saturated aliphatic hydroperoxide. CHP is an aryl hydroperoxide. They are members of a category because the functional characteristic is the reactivity of the hydroperoxide moiety; the aryl/alkyl group is not expected to contribute to the toxicity of the category members as much as the reactivity of the hydroperoxide moiety. Differences in their physical states and some physical-chemical properties are believed to be relevant for exposure scenarios but the common element, the hydroperoxide moiety, is most relevant for toxicity.

1,1-Dimethylethyl hydroperoxide (*tert*-butyl hydroperoxide; TBHP, CAS No. 75-91-2) has previously been assessed in the OECD HPV Programme. Data for TBHP are referenced to provide support for TAHP and CHP. Biodegradation and acute aquatic toxicity endpoints for TAHP are fulfilled using data for TBHP and CHP. Repeated-dose toxicity, chromosomal aberrations, fertility and developmental effects data for TBHP are used to fulfill these endpoints for TAHP and CHP.

The reactivity of organic peroxides is related to their half-lives at a given temperature. When measured at a 0.2 molar concentration in benzene, the temperatures for a 1-hour half-life for CHP, TAHP, and TBHP are 190, 183, and 200 ºC, respectively. The similarity of the activation energies required to decompose these hydroperoxides supports their inclusion as a category because the hydroperoxide moiety is believed to be the primary determinant of the biological effects observed.

According to the draft EU Risk Assessment Report on TBHP for human health, the initial decomposition of these substances is expected to be at the peroxide bond. A key decomposition pathway involves formation of free radicals,

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expected at the site of first contact. The major decomposition product is the rapid formation of t-butanol, which is subsequently metabolized. TBHP is rapidly metabolized *in vivo* to t-butyl alcohol (TBA) by glutathione peroxidase. Cumyl alcohol is the anticipated metabolite of CHP.

CHP, TAHP and TBHP are irritants at the point of administration by ocular, dermal and inhalation routes. A comparison of available subchronic data (TBHP and TBA; CHP) supports the assertion that the toxicity profile for this category of materials is dominated by the irritating to corrosive nature of the peroxide functionality.

The physical properties, reaction profiles and toxicity supports our decision to treat these hydroperoxides as a category, although differences due to different rates of reaction, by-products and chemical structure may be expected.

Physical-chemical properties

CHP, **TAHP** and **TBHP** are liquid preparations at room temperature and pressure. The melting points of **CHP**, **TAHP** and **TBHP** are -9°C, -28.8 °C and -8 °C, respectively. The reported boiling points are 100 - 101 °C at 10.6 hPa and 96 °C at 1013 hPa for **CHP** and **TBHP**, respectively. **TAHP** decomposes at 1013 hPa; TBHP has a decomposition point of 13°C. The density of **CHP**, **TAHP** and **TBHP** are 1.1 g/cm^3, 0.91 g/cm^3 and 0.90 g/cm^3 at 20 °C, respectively. The vapour pressure of **CHP** is 0.02 hPa at 25 °C. The vapour pressure of **TAHP** and **TBHP** are similar (23 hPa at 26°C and 27 hPa at 20°C, respectively). The hydroperoxides are very water soluble, with values ranging from 143,000 (**CHP**) to ≥100,000 (**TBHP**) mg/L. The n-octanol/water partition coefficients (log value) of **CHP**, **TAHP** and **TBHP** are 1.6 at 25 °C (measured), 1.4 (estimated; temperature not specified) and 0.7 at 25 °C (measured), respectively.

Human Health

No data on toxicokinetics are available. Acute toxicity testing has been performed by various routes of exposure for **CHP** (oral), **TAHP** (oral, dermal) and **TBHP** (oral, dermal and inhalation). The inhalation 4-hr LC_{50} (combined sexes) value for **TBHP** in rats was 1.85 mg/L. At all exposure levels, clinical signs of respiratory and ocular irritation were observed, with recovery occurring at the lowest exposure concentration. Lung discoloration was observed during gross necropsy. Valid acute inhalation studies were not available for **TAHP** or **CHP**. The dermal LD_{50} of **TAHP** (OECD TG 402) in rats was 354 mg/kg bw/day (females) and 492 mg/kg bw/day (males). Exposure was 24 hours. Clinical observations included staining around the mouth and on the fur, decreased activity, wobbly gait, reddish colored urine and decreased food consumption. Necropsy of deceased animals revealed congested meningeal vessels in the brain, mottled livers, abnormal contents in the digestive tract, reddened mucosa in urinary bladder and cervical lymph nodes, reddened thymus, and discolored kidneys and spleen. Irritation was observed at the application site. Valid acute dermal toxicity studies were not available for **CHP**. The oral LD_{50} of **TAHP** (OECD TG 401) in rats was 483 mg/kg bw/day (females) and 518 mg/kg bw/day (males). Salivation, abnormal breathing and urine stain were observed in all groups. Necropsy of deceased animals revealed congested meningeal vessels in the brain, mottled livers, abnormal contents in the digestive tract, linear striations and dark red foci in stomach, reddened mucosa in small intestines, dark red and thickened serosa in the stomach, discolored thymus, and abnormally colored contents in urinary bladder and thoracic cavity. The oral LD_{50} for **CHP** was 382 mg/kg bw/day; practically all deaths occurred within 5 days. Extensive urinary bleeding in the rats exposed to 400 mg/kg bw/day was observed during clinical observations.

TAHP is a severe skin irritant that caused necrosis and corrosion in rabbits in a study consistent with OECD Test Guidelines; **TAHP** is a severe eye irritant in rabbits. **CHP** is expected to exhibit similar irritation properties. There are no data available on sensitization for TAHP and CHP.

A repeated-dose inhalation toxicity study is available for **CHP**. Repeated-dose toxicity studies were not available for **TAHP**. However, repeated-dose toxicity studies by the inhalation, dermal and oral route of exposure were available for **TBHP**. In a repeated-dose inhalation toxicity study, rats (10/sex/concentration) were exposed to **CHP** for 6 hrs/day, 5 days/week for 3 months at 0, 1, 6 or 31 mg/m^3 (0, 0.001, 0.006 or 0.03 mg/L, respectively) as an aerosol. The clinical signs of exposure included skin and respiratory irritation. Changes in relative organ weights (heart, liver and kidney) were not considered toxicologically relevant. The NOAEL was 31 mg/m^3 (0.03 mg/L) in this study.

In a repeated-dose toxicity study, rats (12/sex/dose) were exposed by the dermal route to **TBHP** at 0, 22, 44, 88, or 175 mg/kg bw/day for 12 applications over 17 days. Dermal irritation (confirmed by histopathological findings) was observed. No other clinical signs of toxicity were observed. The NOAEL for dermal toxicity for **TBHP** in rats was 88 mg/kg bw/day (males) and 44 mg/kg bw/day (females). Due to the limited number of systemic endpoints measured, this is primarily a NOAEL for dermal effects. In a similar study, mice (5/sex/dose) were administered 0, 22, 44, 88, 176 or 352 mg/kg bw/day for 13 applications over 18 days. Dermal irritation at the application site was the only clinical sign of toxicity; confirmed by histopathological findings. The NOAEL for **TBHP** for dermal toxicity in mice was 44 mg/kg bw/day (males) and 88 mg/kg bw/day (females).

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In a combined repeated-dose/reproductive/developmental (OECD TG 422) toxicity study, rats (12/sex/dose) were administered **TBHP** by oral gavage for 41-45 days at doses of 0, 3, 10 and 30 mg/kg bw/day. Treatment-related changes in the form of tubular nephrosis, as well as multifocal, increased accumulation of tubular proteinaceous material, were observed in kidneys of male rats at 10 and 30 mg/kg bw/day. This accumulation of intratubular protein is considered a male rat characteristic. In males, the bilirubin level increased but was decreased in females at doses of 10 mg/kg bw/day and above. The reported NOAEL for systemic toxicity was 3 mg/kg bw/day based on kidney effects attributed to alpha-2µ-globulin accumulation as previously concluded in the OECD HPV Programme.

In a reverse mutation assay in several *S. typhimurium* strains, **CHP** was mutagenic or weakly mutagenic. **CHP** was mutagenic in strain TA98 at one dose level with rat S9, in a single run with mouse S9 and in one of two experiments without activation. **TAHP** (OECD TG 471) did not induce a significant increase in the number of revertant colonies over that shown in the solvent control plates for strains TA1537, TA1535, TA1538, and TA98 with or without metabolic activation. However, for TA100 there was a slight increase (less than 2 fold) in the number of revertants. In a mouse lymphoma study, **TBHP** induced a dose-dependent increase in the mutant frequency of cultures treated both with and without metabolic activation. In a mammalian cell gene mutation assay, **TAHP** did not induce mutations at the HGPRT locus in CHO cells. **TBHP** was positive in several chromosome aberration studies with cultured mammalian cells. *In vitro* chromosome aberration studies were not located for **TAHP** and **CHP**. In a mouse micronucleus test, **TBHP** did not result in chromosomal damage and/or damage to the mitotic apparatus in bone marrow cells of mice *in vivo*. In an *in vivo* mammalian bone marrow chromosome aberration test, **TBHP** did not induce chromosomal damage when administered to rats by inhalation for 5 d. *In vivo* genotoxicity studies were not located for **TAHP**. In studies with mice, similar to OECD TG 478, repeated intraperitoneal injection of **TBHP** for males resulted in a significant increase in DNA damage in the testicular tissue at doses of 27 and 54 mg/kg bw/day and above; injection of **CHP** for males resulted in the same effects at doses of 23 and 46 mg/kg bw/day and above. Based on these results, **TAHP** and **CHP** are considered to be potentially genotoxic *in vitro*. **TBHP** is considered genotoxic *in vitro*, and potentially genotoxic *in vivo*.

Reliable carcinogenicity studies were not available for **CHP** or **TAHP**.

No reproductive/developmental toxicity data are available for **TAHP** or **CHP**. In an OECD TG 422 study with **TBHP** in rats described above, the body weight of pups, clinical and macroscopic observations were comparable to controls. No treatment related effects were observed. Based on these data, the NOAEL for reproductive toxicity was 30 mg/kg bw/day (the highest dose tested). The NOAEL for developmental toxicity was 30 mg/kg bw/day as previously concluded in the OECD HPV Programme.

In a developmental toxicity study (OECD TG 414), rats (24 females/dose) were exposed to **TBHP** at 0, 5, 15 and 50 mg/kg bw/day by oral gavage once/day from days 6 to 15 of gestation. There was a slight decrease in maternal body weight gain and food intake at 50 mg/kg bw/day. The NOAEL for developmental toxicity was 50 mg/kg bw/day (highest dose tested). Overall, **TAHP** and **CHP** are not likely to exhibit reproductive/developmental toxicity based on available information.

The available data suggest chemicals in this category possess properties indicating a hazard for human health (acute inhalation toxicity, corrosivity, genotoxicity, repeated-dose toxicity for the oral, dermal and inhalation exposure routes). Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD HPV Programme.

Environment

Photodegradation half-lives for **CHP**, **TAHP** and **TBHP** range from ca. 1 to 5 days. **TBHP** was photolysed (250 - 390 nm) in a quartz cell alone or in 2.5% solution of aliphatic solvents; a high **TBHP** radical concentration formed during photolysis alone or in solvent. EUSES calculations suggest a first-order degradation rate constant of 0.13/day for **TBHP** in air.

The stability of hydroperoxides in pure water does not represent the situation under real-world conditions. In the presence of transition metals or other reducing agents, hydroperoxides rapidly decompose. In natural waters containing transition metals and organic matter, hydroperoxides, and organic peroxides in general, are not expected to be stable.

An abiotic degradation study with **TBHP** (similar to OECD TG 111) did not show an appreciable degradation during the 5-d test period at a temperature of 50 ^{o}C and pH values of 4, 7 and 9, respectively. The abiotic degradation of **TBHP** was studied in 10-d tests in ultra-pure water and in sterilised (thus abiotic) activated sludge; the results show up to around 5% degradation of **TBHP** in ultra-pure water and up to around 25% degradation in sterilised sludge.

Level III Fugacity modeling, using loading rates for Air, Soil, and Water of 1000 kg/h for each medium, shows the

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following percent distribution: **CHP**: Air = 1.1%; Soil = 65%; Water = 34%; Sediment = 1.5%; **TAHP**: Air = 6.7%; Soil = 47%; Water = 46%; Sediment = 0.09%; **TBHP**: Air = 7.7%; Soil = 42%; Water = 51%; Sediment = 0.88%.

CHP did not readily degrade over 28 days under the test conditions of an OECD TG 301 B. In OECD TG 301 B and D tests, there was no biodegradation of **TBHP** over 28 days. No measured data are available for TAHP, but based on its structural similarity to TBHP, it is not likely to be readily biodegradable.

The estimated BCF for **TBHP**, **TAHP** and **CHP** are 3.2, 2.5 and 9.1, respectively; these materials have minimal potential for bioaccumulation.

The toxicity of **CHP** to groups of *Oncorhynchus mykiss* was evaluated in an OECD TG 203 study. The interpolated LC_{50} value was 3.9 mg/L and the 96-h NOEC (behavioural changes) was < 1.5 mg/L. Because the last fish in the 6 mg/L group died in the last 24 hours of the study, the reported LC_{50} may not be asymptotic. In an OECD TG 202 study with **CHP**, where the test article was shown by measurements to be stable over the 24-hour renewal period, the 48-hr EC_{50} for *Daphnia magna* was 18 mg/L and the 48-hr NOEC was 10 mg/L. In an OECD TG 201 study, *Pseudokirchneriella subcapitata* were exposed to **CHP** for 72 hours; the EC_{b50} was 1.6 mg/L and the 72-hr EC_{r50} was 3.1 mg/L. The reported LOEC and NOEC for biomass and growth rate were 1 and 2.2 mg/L (biomass), and 0.46 and 1.0 mg/L, respectively. Reported values were nominal concentrations.

The toxicity of **TBHP** was evaluated in OECD TG 203 studies with *Pimephales promelas* or *Poecilia reticulata* exposed under measured semi-static conditions for 96 hours. The 96-hr LC_{50} and NOEC for *Pimephales promelas* were 42.3 and 32 mg/L, respectively. In the second 96-hr fish study, the LC_{50} and NOEC values for *Poecilia reticulata* were 57 and 30 mg/L, respectively. In an OECD TG 202 study, the 48-hr EC_{50} for *Daphnia magna* exposed to **TBHP** was 20 mg/L and the NOEC was 10 mg/L. Reported values were nominal concentrations. In an OECD TG 201 study, *Pseudokirchneriella subcapitata* were exposed to **TBHP** for 72 hours; the EC_{50} with respect to growth rate and biomass were 2.1 and 1.2 mg/L. The NOEC for growth rate and biomass was 0.32 mg/L. Reported values are nominal concentrations.

ECOSAR estimations of toxicity to fish, daphnia and algae are available. **CHP**: LC_{50} for fish = 0.26 mg/L, daphnid = 5.1 mg/L; **TAHP**: LC_{50} for fish = 0.14 mg/L, daphnid = 7.1 mg/L; **TBHP**: LC_{50} for fish = 0.11 mg/L, daphnid = 9.8 mg/L. There are no predicted values for algae.

The available data suggest chemicals in this category are not readily biodegradable and possess properties indicating a hazard for the environment (acute toxicity to fish, invertebrates and algae between 1 and 100 mg/L). However, they possess a minimal potential for bioaccumulation with estimated BCFs less than 10. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Worldwide production of neat **CHP** in 2006 was in the range of 1,000-10,000 tonnes. **CHP** is used as a modifier with certain resins, a polymerization initiator and as a raw material to make other organic peroxides and resins. Approximately 790 tonnes of neat **TAHP** and approximately 26,400 tonnes of neat **TBHP** were produced worldwide in 2006. Both are used as a source of free radicals in polymerization and other reactions, in the manufacture of other peroxides, and as an emulsion polymerization initiator.

Releases to the environment and potential industrial worker exposure can occur during handling in industrial settings, including manufacture (open vessel), use and spills. Exposure limits have not been established, but internal industrial hygiene limits are used within industrial facilities.

Consumer exposure is expected to be extremely low because only negligible amounts of hydroperoxide are expected to remain after its use in processing of materials based on application of the Arrhenius equation. During manufacturing processes in which hydroperoxides are used, the process materials are typically held at a thermal decomposition temperature for many half-lives, and therefore only negligible amounts of the hydroperoxides are expected to remain. Manufacturers provide customers with data sheets showing half-lives as a function of temperature so they can select appropriate process temperatures and holding times. It is important to manufacturers of articles using hydroperoxides to ensure the hydroperoxides are reacted, until only negligible amounts remain, to avoid post-processing changes in material properties.

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