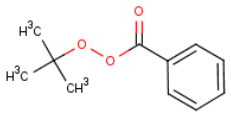
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	614-45-9
Chemical Name(s)	t-Butyl peroxybenzoate (**TBPB**)
Structural Formula(s)	 **TBPB**

SUMMARY CONCLUSIONS OF THE SIAR

Physical-chemical Properties

TBPB is a liquid with a melting point of > 9 to < 11 °C (measured; technically pure); a measured boiling point is not available as the substance decomposes. The self-accelerating decomposition temperature (SADT) for TBPB is 60 °C. A vapour pressure of 0.003 Pa at 20 °C (extrapolated from measured data) is available for technically pure TBPB. The measured octanol-water partition coefficient (log K_{ow}) of technically pure TBPB is 3 at 25 °C. The measured water solubility of technically pure TBPB is 325 mg/l at 20 °C.

Reactivity

Organic peroxides contain an unstable O-O bond, and as such these substances are used as free radical formers to initiate reactions (opening of vinylic bonds, abstraction of hydrogen, etc. Formation of free radicals through the cleavage of the O-O bond is typically accomplished by increasing the temperature. Peroxyesters are a class of organic peroxides that are relatively unstable under basic or acidic conditions in the presence of water, which catalyzes the cleavage of the peroxyester molecule to form an organic acid and conjugate hydroperoxide. Many peroxyesters cannot be produced in the absence of a diluent due to safety concerns.

TBPB is a stable organic peroxide and can be produced in the absence of diluent. Most tests have been performed with technically pure TBPB, with typical purity >98%.

Human Health

Toxicokinetics

Toxicokinetic data are available for TBPB. *In vitro* studies suggest technically pure TBPB binds to or is absorbed through skin. TBPB was unstable in rat and human blood, with half lives of 10.4 and 4.0 minutes, respectively. In rat liver microsomes and a rat soluble enzyme preparation, less than 1% TBPB was found after 15 minutes. Benzoic acid (CAS No. 532-32-1) and t-butanol (CAS No. 75-65-0) made up 93% of the major degradation/metabolic products.

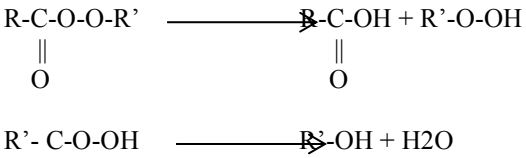
In vivo studies determined that approximately 16% of dermal doses administered to rats were absorbed and rapidly eliminated without tissue accumulation. In intact animals, the major decomposition product detected in the rinse or extract of all skin samples was benzoic acid. Technically pure TBPB given intravenously was rapidly degraded and eliminated, primarily in urine, with no apparent accumulation in any tissue.

Peroxidase activity

Peroxidases are enzymes that act as catalysts to promote the oxidation of substances. Peroxidases act on naturally occurring peroxides (such as hydrogen peroxide) forming an acid, alcohol and water as shown below.

ROOR' + electron donor (2 e-) + 2H+ → ROH + R'OH

For peroxyesters:



Peroxidases are commonly found in plants and animals, including humans. Based on data for other organic peroxides, peroxidase is presumed to be the active enzyme in TBPB metabolism. TBPB is expected to be oxidized by naturally occurring peroxidases, resulting in the cleavage of the O-O bond. The expected metabolic products of TBPB are benzoic acid and t-butyl hydroperoxide. The peroxidase will also cleave the O-O bond of the hydroperoxide to form water and the corresponding alcohol t-butanol. Hydrolysis and enzymatic cleavage of the parent molecule are separate and competing reactions that occur simultaneously in an aqueous biological environment. The expectation is that enzymatic reaction will readily occur with the parent molecule and any hydroperoxy byproducts.

Acute toxicity

The 4-hour LC_{50} for technically pure TBPB aerosol was between 1.01 and 4.9 mg/L (measured concentrations) in male and female rats [OECD TG 436]. All animals in the 4.9 mg/L group died; there were no deaths at 1.01 mg/L. Clinical signs for TBPB at both concentrations included evidence of respiratory irritation (labored breathing, tachypnea). At 1.01 mg/L, clinical signs disappeared after 3 days. Incompletely collapsed lung and dark red or reddish discoloration of the lung or the thymus were seen at 4.9 mg/L during necropsy; no macroscopic findings at 1.01 mg/L were noted.

The acute dermal LD_{50} for rats was > 2000 mg/kg bw for technically pure TBPB [OECD TG 402]. Signs of local (site of contact) irritation were noted **(**slight generalized erythema, slight to moderate desquamation, and localized necrotic areas).

The acute dermal LD_{50} for rabbits was also > 2000 mg/kg bw for technically pure TBPB [no guideline specified].

The acute oral LD_{50} for rats was > 2000 mg/kg bw of technically pure TBPB [OECD TG 423]**.** There were no deaths, no effects on body weight and no findings at necropsy.

Irritation

Technically pure TBPB was irritating to rabbit skin in one study (the 72 hour mean Draize scores for erythema and edema were 3.5 and 1.3, respectively), but found not irritating in second test (Draize scores not available) [OECD TG 404 or similar]. Based on the worst case approach, and taking into account effects observed in acute dermal toxicity studies (OECD TG 402), TBPB is considered to be a skin irritant. Two eye irritation studies showed that technically pure TBPB is not an eye irritant (the 72 hour mean Draize scores for redness and chemosis were each 0.7 in one study; the Draize scores were not available in the second study) [OECD TG 405 or similar]. TBPB may be a respiratory irritant based on findings in the respiratory tract in an acute aerosol inhalation study [OECD TG 436] with rats.

Skin sensitization

Technically pure TBPB was found to be a skin sensitizer in Local Lymph Node Assay [OECD TG 429]. No sensitizing potential was found in an older Buehler test. Based on the OECD 429 (key study), TBPB is considered to be a skin sensitizer.

Repeated dose toxicity

In a National Toxicology Program (NTP) study, rats were administered technically pure TBPB in water via oral gavage at 0, 30, 60, 125, 250, or 500 mg/kg bw/day for 5 days/week for 13 weeks. One female in the 250 mg/kg bw/day group died and a control female was removed because it had been mis-sexed. At 500 mg/kg bw/day, females had reduced food consumption and decreased body weight gains. Increased forestomach weights were observed at >=60 mg/kg bw (females) and >= 250 mg/kg bw/day (males). Increased glandular stomach weights and decreased spleen weights were observed at 500 mg/kg bw. Clinical chemistry or hematology were not examined. Histopathological changes of the forestomach including hyperplasia, microhemorrhages, edema, neutrophil infiltration were observed at >= 60 mg/kg bw. Based on forestomach changes at 60 mg/kg bw/day and higher, the No Observed Adverse Effect Level (NOAEL) is 30 mg/kg bw/day for male and female rats.

In an NTP study, mice were administered technically pure TBPB in water via oral gavage at of 0, 30, 60, 125, 250, or 500 mg/kg bw/day 5 days per week for 13 weeks. One control male died of apparent gavage error, and a female in the 250 mg/kg bw/day dose group died. There was no effect on food consumption or body weight, no clinical signs or findings at gross necropsy. Organ weight changes included increased forestomach weights at >= 250 mg/kg bw/day, increased glandular stomach weights at 500 mg/kg bw/day (females only), and increased glandular stomach-to-body-weight ratios at 250 mg/kg bw/day (females only). Clinical chemistry or hematology were not examined. Hyperplasia of the stratified squamous epithelium of the forestomach (increased cellularity and basophilia of the squamous epithelium, with hyperkeratosis) increased in frequency and severity with increasing doses >= 60 mg/kg bw/day for both sexes; only 1/10 males at 30 mg/kg bw/day showed hyperplasia, which was minimal in severity). Based on induction of forestomach lesions in mice at 60 mg/kg bw/day and higher, the NOAEL is 30 mg/kg bw/day.

Mutagenicity

One gene mutation test *in vitro* (*S. typhimurium* strains TA100, TA1535, TA1537, TA98 and TA1538, similar to OECD TG 471) was found positive and a second similarly conducted gene mutation test was negative. Two sister chromatid exchange tests *in vitro* with mammalian Chinese Hamster Ovarian (CHO) cells (similar to OECD TG 479) were positive. A mammalian mouse lymphoma assay was positive. Technically pure TBPB was also positive in a mouse lymphoma assay, but without information on colony sizing it is not clear whether the results represent gene mutations or chromosomal aberrations. Technically pure TBPB was negative in an *in vivo* micronucleus assay; no information was available to indicate whether TBPB reached the bone marrow. TBPB is considered to be mutagenic and clastogenic *in vitro*. No information on gene mutation *in vivo* is available.

Carcinogenicity

No conventional carcinogenicity studies were located for TBPB; however, it was evaluated for its ability to increase biomarkers of tumor promotion in mouse skin and to produce mutations involved in the initiation of mouse skin tumors. Technically pure TBPB exhibited significant increases in all three biomarkers associated with tumor promoting activity (sustained epidermal hyperplasia, dermal inflammation and oxidative DNA damage). TBPB did not cause detectable mutations in the c-Ha-ras proto-oncogene **(**mutations involved in the initiation of mouse skin tumors**).** TBPB is not likely to possess tumor-initiating activity.

Reproductive toxicity

Effects on fertility

In an OECD TG 421 study with technically pure TBPB, rats received the test substance in corn oil by oral (gavage) at dose levels of 0, 100 300, 750 (males) and 1000 (females) mg/kg bw. The parental NOAEL is 300 mg/kg bw/day based on one death and clinical signs in dams, and reduced food consumption and body weight gain in males. Based on the absence of reproductive effects, the NOAEL for fertility was 750 (males) or 1000 (females) mg/kg bw/day (highest doses tested).

Developmental toxicity

In an OECD TG 414 study, groups of 24 timed-mated female rats were administered technically pure TBPB by oral gavage at doses of 0, 100, 300 and 1000 mg/kg bw/day from Day 3 (prior to implantation) to Day 19 of gestation (day prior to expected parturition). There were no deaths. Salivation was noted primarily in the 1000 mg/kg bw/day group. At 1000 mg/kg bw/day, body weight gain was generally lower than control throughout gestation, and was still apparent after values were adjusted for the contribution of the gravid uterus. Food consumption was generally lower at 1000 mg/kg bw/day between Day 3 and Day 8 of gestation. Significant clinical signs, body weight effects and effects on food consumption were not observed at 100 and 300 mg/kg

bw/day. There were no maternal findings at gross necropsy. *In utero* survival of the developing conceptus appeared unaffected by maternal treatment at 1000 mg/kg bw/day with both pre and post-implantation losses being lower than control. This was despite a clear reduction in fetal weight which resulted in lower litter weight at this dosage. The lower fetal weight at 1000 mg/kg bw/day is suggestive of a retardation of fetal growth at this dosage and this was supported by subsequent findings observed at fetal examination. Externally many of the fetuses appeared small and there was a plethora of skeletal findings indicating incomplete ossification or no ossification for many regions of the skeleton. Visceral findings included non-uniform patterning of the rugae, kinked/dilated ureter(s), increased renal pelvic cavitation, absent renal papila and partially undescended thymus lobe. These visceral findings were also considered to indicate a retardation of fetal growth. Litter data, fetal, litter and placental weights, external fetal appearance and detailed skeletal fetal evaluation did not indicate any obvious effect of maternal treatment on the developing conceptus at 300 mg/kg bw/day. However, visceral examination of the fetuses in the 300 mg/kg bw/day group showed a non-statistically significant increased incidence of fetuses/litters with kinked/dilated ureter(s) as compared to recent background control incidence. The No Observed Effect Level (NOEL) for the developing conceptus is 100 mg/kg bw/day; kinked/dilated uretus are considered considered reversible variations and therefore not considered adverse; the NOAEL for the developing conceptus was 300 mg/kg bw/day. The maternal NOAEL was 300 mg/kg bw/day, based on lower maternal body weight gain during gestation and an initial effect on food consumption at 1000 mg/kg bw/day.

In the OECD TG 421 study described above, the number of live pups at first litter check and on day 4 post-partum was unaffected. No test item-related clinical signs were noted at first litter check and during the lactation. Based on the lower mean pup weight (16%) at 1000 mg/kg bw/day, the NOAEL for developmental toxicity is considered to be 300 mg/kg bw/day.

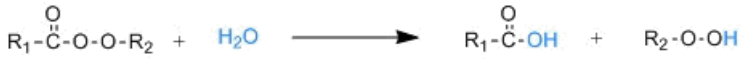
TBPB possesses properties indicating a hazard for human health (acute toxicity via inhalation, skin irritation, respiratory irritation, skin sensitization), mutagenicity (gene mutations and chromosomal aberrations *in vitro*), repeated dose toxicity, and developmental toxicity at high doses. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment

Modeling results from EPIWIN should be interpreted with caution as the library of reference peroxide substances used is very limited in number.

In an OECD TG 111 study conducted with TBPB, the hydrolysis half-life of TBPB as a technically pure substance at pH 7 and 30^{o}C is 21 days. The extrapolated half-life for pH 7 at 25 ^{o}C was 41 days, suggesting that TBPB does not hydrolyze rapidly in the natural environment.

A general hydrolysis reaction scheme of a peroxyester is shown below.



The hydrolysis rate is not expected to be sufficiently rapid to influence the toxicity of this substance. That is, test organisms are likely to be exposed to parent substance rather than a mixture of parent, as well as hydrolysis products. The expected hydrolysis products of TBPB are Benzoic acid (CAS No 532-32-1) and tert-Butyl hydroperoxide (CAS No 75-91-2).

In the atmosphere, indirect photo-oxidation by reaction with hydroxyl radicals is expected to occur with a half-life of 5 days for TBPB. Technically pure TBPB is readily biodegradable (72% after 28 days (did not meet the 14 day window) and 70% after 28 days (60% biodegradation within 14 day window) in OECD TG 301D tests.

EPIWIN Level III (Full Output) fugacity modeling predicts that, when distributed equally to air, water and soil, TBPB will partition primarily to water and soil, with lesser amounts partitioning to air. These results should be interpreted with caution as the library of reference peroxide substances used in EPIWIN is very limited in number.

An estimated Henry's Law Constant (HLC) of 20.8 Pa-m^3/mol (Bond estimate) at 25 ^{o}C suggests that

volatilization of TBPB from the water phase is expected to be moderate. These results should be interpreted with caution as the library of reference peroxide substances used in EPIWIN is very limited in number. Using user-entered vapor pressure and water solubility values, the HLC based on VP/Wsol estimate is 0.0018 Pa-m^3/mol.

The estimated BCF value (using BCFBAF v3.01) of 44.3 indicates that TBPB is not expected to bioaccumulate. These results should be interpreted with caution as the library of reference peroxide substances used in EPIWIN is very limited in number and the kM module (whole body primary biotransformation half-lives rate constant) does not contain peroxyester fragments. TBPB is not anticipated to be bioaccumulative based on the log Kow of 3.0. Additionally, the reactivity of TBPB is expected to mitigate its potential for bioaccumulation.

Aquatic toxicity

The following acute toxicity test results have been determined for aquatic species:

Substance	Species	Result	Study Design
Fish, acute toxicity			
TBPB (technically pure)	*Danio rerio*	96 h LC_{50} = 1.6 mg/L (measured)	OECD TG 203 (Fish, Acute Toxicity Test); semi-static
Aquatic invertebrate, acute toxicity			
TBPB (technically pure)	*Daphnia magna*	48 h EC_{50} = 11 mg/L (measured)	OECD TG 202 (Daphnia sp. Acute Immobilisation Test); static
Aquatic plants, acute toxicity			
TBPB (technically pure)	*Pseudokirchneriella subcapitata*	72 h ErC_{50} = 0.80 mg/L (measured) 72 h EyC_{50} = 0.40 (measured)	OECD TG 201 (Alga, Growth Inhibition Test); static

In a 21-day reproductive toxicity test with Daphnia, the NOEC for technically pure TBPB for reproduction and parental length and weight was 0.44 mg/L (based on measured concentrations).

In an OECD TG 209 (Activated Sludge, Respiration Inhibition Test), the 30 minute EC_{50} for activated sludge was 43 mg/L.

TBPB possesses properties indicating a hazard for the environment (acute toxicity from <1 mg/L for aquatic plants, and between 1-100 mg/L for fish and aquatic invertebrates, chronic toxicity to aquatic invertebrates <1 mg/L). TBPB was readily biodegradable and is not expected to bioaccumulate. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD HPV Programme.

Exposure

Based on the 2006 Inventory Update Reporting Rule (IUR), production volumes in the United States were 453 to < 4536 tonnes.

According to the ECHA registration dossier, EU production of **TBPB** is currently 1,000 – 10,000 tonnes per annum (data for 2014).

During manufacture, peroxyesters are handled in closed systems with the exception of packing processes, where engineering measures (local ventilation) would be used. Personal protective equipment includes chemical goggles, and if any lines are opened, chemical gloves are used. Inhalation and dermal would be the most likely routes of exposure. At the industrial level, the peroxyesters are used in bulk in dilute solution in closed systems. Engineering measures (local ventilation) are used. Inhalation and dermal would be the most likely routes of exposure. When used in more concentrated forms, the containers are 7.5 gallons (ca. 30 L) or less. Personal protective equipment include chemical goggles, and if any lines are opened, chemical gloves. TBPB is used as a polymerization initiator in the manufacture of various polymers (PVC, polyolefin, etc.). Most organic peroxides are used at levels around 1% in an industrial setting (which is also the case for TBPB), and may be produced and used with diluents [a diluent is an ingredient used to reduce the concentration of an active ingredient to achieve the desired effect of keeping the temperature down, and may also be referred to as

a heat sink, which is a reservoir that absorbs heat as energy]. TBPB is consumed during the polymerisation reaction. There are unlikely to be any sources of environmental exposure. TBPB is not used in consumer products, but is used to make polymer resins that may be manufactured into consumer products. TBPB is expected to be completely consumed during resin manufacture and polymer article production, are therefore not expected to be present as residuals in consumer products.

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