# SIDS INITIAL ASSESSMENT PROFILE

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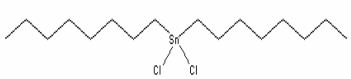
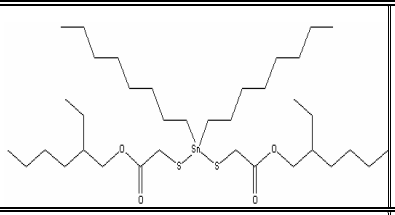
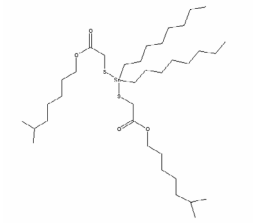
|---|---|---|
| **Chemical Category** | Dioctyltin dichloride and selected thioesters | |
| **Structural Formulas Chemical Names and CAS Registry Numbers** |  | Dioctyltin dichloride<br>[DOTC] CASRN 3542-36-7 |
| |  | Dioctyltin bis(2-ethylhexyl thioglycolate)<br>[DOT(EHTG)] CASRN 15571-58-1 |
| |  | Dioctyltin bis(isooctyl thioglycolate)<br>[DOT(IOTG)] CASRN 26401-97-8 |

## SUMMARY CONCLUSIONS OF THE SIAR

**Category Rationale**

DOTC, DOTC(EHTG), and DOT(IOTG) are considered one category of compounds for mammalian toxicology studies via the oral route. The justification for this category is based on structural similarities and the demonstrated rapid conversion of the thioesters to DOTC when placed in simulated mammalian gastric contents [0.07 M HCl] under physiological conditions. For DOT(EHTG), 100% conversion to DOTC occurred within 0.5 hours. Thus, MOTC is the appropriate surrogate for mammalian toxicology studies via the oral route.

Sensitization, irritation and *in vitro* genotoxicity are not covered under the category approach and the results of the mammalian *in vivo* tests via the oral route with the representative chloride cannot be extrapolated to the dermal or inhalation routes. However, the esters have much higher molecular weight and lower volatility than the chlorides, reducing the possibility of toxicity via inhalation and dermal routes.

The category approach was not used for the ecotoxicity and environmental fate endpoints. The considerable differences in the structures of the labile ligands cause differences in water solubility between the alkyltin chloride and thioesters affecting their respective bioavailabilities and distribution in the environment. Furthermore, DOT(EHTG) and DOT(IOTG) will degrade in aqueous solution such that organisms will be exposed to the parent material and their different degradation products. DOTC is not an appropriate surrogate for the thioesters for the ecotoxicity and environmental fate endpoints.

**Analogue Rationale**

Data for DOT(EHTG) and DOT(IOTG) are used interchangeably because they are isomers differing only slightly in the structure of the C-8 alcohol of the mercaptoester ligand. In addition, the breakdown products of DOT(EHTG) and DOT(IOTG) are the thioglycolate esters (EHTG and IOTG), which have the common degradates, thioglycolic acid and C-8 alcohols (either 2-ethylhexanol or isooctanol). EHTG and IOTG also have similar physicochemical and toxicological properties.

EHTG (CAS No. 7659-86-1) and IOTG (CAS No. 25103-09-7) form the Thioglycolic Acid Esters B Category, assessed in the OECD HPV Chemicals Program.

**Human Health**

The majority of toxicology studies were conducted with commercial mixtures having high dialkyltin to monalkyltin ratios.

No toxicokinetic data are available for dioctyltins. However, a study under simulated gastric conditions was conducted with DOT(EHTG) (described above). *In vitro* data for DOTC and DOT(EHTG) indicate the dermal penetration of these dioctyltins is low. The acute inhalation LC50 for DOTC in rats is 390 mg/$m^3$ for a 1-hr aerosol exposure to particles sizes of 3-10 microns, and 37,000 mg/$m^3$ for a 1-hr aerosol exposure to particles sizes of 2.5-3.5 microns. The acute inhalation LC50 of DOT(EHTG)/(IOTG) is 470 mg/m3 in a study assigned a reliability of 4. The acute dermal LD50 of DOT(EHTG)/(IOTG) is > 2000 mg/kg bw in rats; there are no acute dermal toxicity data for DOTC. Acute oral LD50 values are 3300–>7926 mg/kg bw in rats for DOTC, approx. 2000 mg/kg bw in rats and mice for DOT(EHTG), and 1120–3800 mg/kg bw in rats and 133-1400 mg/kg bw in mice for DOT(IOTG).

DOTC was not a primary skin or eye irritant in animal studies; DOT(EHTG) was found to be a irritating to the skin and eyes of test animals; and undiluted DOT(IOTG) was slightly irritating to the skin and not irritating to the eyes of test animals. No data on sensitization are available on DOTC, but the hydrolysis products EHTG or IOTG are sensitizers. DOT(EHTG)/(IOTG) was a skin sensitizer in two OECD TG 406 studies.

There are no repeated dose studies for DOTC, DOT(EHTG) or DOT(IOTG) via the dermal or inhalation routes.

The repeated dose toxicity of DOTC has been evaluated in a number of studies of varying duration. In the critical study for this endpoint, DOTC (92.1% purity) was evaluated in a GLP 90-day dietary study (OECD TG 408). The NOAEL for sub-chronic toxicity could not be established for this study, and the LOAEL was 10 ppm diet (0.7 mg/kg bw/day). The critical treatment-related changes included a reduction of thymus weight at all doses (10, 100, and 300 ppm diet) and lymphoid depletion of the thymus at 100 (6.5-6.8 mg/kg bw/day) and 300 ppm (19.3-19.8 mg/kg bw/day) diet. Other treatment-related effects included changes in clinical chemistry (ALP, bilirubin, cholesterol, total protein, bile acids, phospholipids, calcium, sodium, A/G ratio), hematology (Hb, PCV, MCV, MCH, reticulocytes, prothrombin time, lymphocytes, monocytes, total WBC), urinalysis (urinary crystals), and changes in organ weights (adrenals, thymus, spleen, kidneys, testes). Histopathological changes observed in the thymus included lymphoid depletion, characterized by a decrease in the size of the thymic lobules which can be ascribed to extensive loss of cortical and medullary small lymphocytes. Consequently, the distinction between the cortical and medullary areas was blurred. Although not accompanied by histopathological effects, the reduction of absolute and relative thymus weights in females at 10 ppm (0.7 mg/kg bw/day) was considered toxicologically relevant. An analysis of the critical toxic effect in this study (absolute and relative thymus weights of females) was performed using Benchmark Dose software developed by EPA; a putative NOAEL of 0.45 mg/kg/day was recommended for DOTC.

No NOAEL was determined in a 6-week dietary study of DOTC (>98% purity) in male and female rats, and the LOAEL was determined to be 50 ppm diet (estimated at 2.5 mg/kg/day). In the 6-week study, treatment-related thymic changes included thymic atrophy and lymphocyte depletion in the thymus-dependent paracortical areas of peripheral lymph nodes. In a 2-week dietary study of DOTC in male rats, 50 or 150 ppm in the diet resulted in reduced thymus and spleen weights (LOAEL was 50 ppm diet, estimated at 2.5 mg/kg/day).

Two 90-day repeated dose oral toxicity studies of DOT(EHTG) resulted in NOAELs of 10 ppm (0.5 mg/kg/bw/day) and 25 ppm (estimated at 1.25 mg/kg/day) in the diet. Both studies reported reductions in thymus weights (≥25 ppm diet). Thymic atrophy and lymphoid depletion were reported at ≥ 100 ppm diet (approximately 7 mg/kg bw/day). For DOT(IOTG), a 30-day repeated dose oral study in male rats and a 90-day repeat dose oral study in male and female rats reported NOAELs of 25 ppm diet (approximately 1.25 mg/kg bw-day) and 150 ppm diet (approximately 3.8-12.2 mg/kg bw-day for males, and 4.8-12.8 mg/kg bw/day for females); effects on the thymus were not investigated in either of these studies.

DOTC, DOT(EHTG) and DOT(IOTG) were negative in 4 of 16 *in vitro* genetic studies, including standard Ames assays (all), HGPRT assays (DOTC), a point mutation test (DOTC), and DNA binding and repair studies

(DOTC). DOTC was positive in the absence of metabolic activation in an in vitro mouse lymphoma assay and a gene mutation assay with *Saccharomyces cerevisiae*. DOT(EHTG) was weakly positive in the absence of metabolic activation to *S. typhimurium* strain TA100. DOTC was negative in an *in vivo* mouse micronucleus assay (OECD TG 474) and an *in vivo* DNA-binding assay, and did not increase the number of sister chromatid exchanges. A DOT(IOTG):MOT(IOTG) (80:20) mixture was negative in two *in vivo* mouse micronucleus assays. No *in vivo* genetic study of DOT(EHTG) was conducted; however, data for the analogue DOT(IOTG) is relevant for this endpoint. Based on these observations the overall conclusion is that DOTC does not have genotoxic potential.

The potential reproductive and developmental toxicity of DOTC was investigated in rats in an OECD TG 421 study. DOTC was maternally toxic at all dose levels – 10 (0.5-0.7 mg/kg bw/day), 100 (4.2-6.2 mg/kg bw/day) and 300 ppm diet (8.4-17.0 mg/kg bw/day). One or 2 animals of the 100 ppm and 300 ppm groups showed indications of treatment-related clinical effects, i.e., thin, pale appearance, piloerection and blepharospasm. Body weights were reduced at 100 and 300 ppm diet, thymus weights were decreased 33-38% at 100 ppm diet and 62-69% at 300 ppm diet, and severe to very severe treatment-related lymphoid depletion in dams was observed in the 10 ppm (5/10 animals), 100 ppm (10/10 animals), and 300 ppm (10/10 animals) dietary groups. The NOAEL for maternal toxicity was not established in this study, and the LOAEL was 10 ppm diet (0.5-0.7 mg/kg bw/day).

Treatment-related effects of DOTC on reproduction and development (OECD TG 421) of the pups were limited to the 100 and 300 ppm groups. Effects at 100 ppm diet included decreased gestation index (71% vs. 86% in controls), decreased live birth index (53% vs. 99%), decreased viability index (74% vs. 94%), increased post-implantations loss (49.2% vs. 22.3%), increased number of runts (PN1 and 4), and 2 dams delivered only dead pups. At 500 ppm diet, treatment-related effects included decreased gestation index (50% vs. 86% in controls), decreased live birth index (60% vs. 99%), decreased viability index (12% vs. 94%), increased post-implantations loss (70% vs. 22.3%), increased number of runts (PN1 and 4), and 1 dam delivered only dead pups. The NOAEL for reproduction and developmental effects was 10 ppm diet (0.5-0.7 mg/kg bw/day); LOAEL was 100 ppm diet (4.2-6.2 mg/kg bw/day ).

A 2-generation study and developmental toxicity studies in mice, rats and rabbits with mixed DOT(IOTG):MOT(IOTG) (78.8:16.9, 80:20 ratio) showed maternal effects on the thymus, dose-related developmental abnormalities of bone formation in mice and rabbits, increased post-implantation losses, and decreased fetal weight plus decreased fetal viability in mice and rabbits. Compared to the screening study with DOTC, the conclusion was that in the comparable period of pregnancy, the effects on fetal weight and viability were basically the same. In contrast, rats did not show any of the abnormalities of bone formation seen in mice and rabbits.

In the 2-generation study with the DOT(IOTG):MOT(IOTG) mixture (78.8:16.9) the NOAEL for the F0 and F1 generations was 20 ppm (1.5 mg/kg bw/day), and the LOAEL was 60 ppm (4.7 mg/kg bw/day), based on reduced thymus weights of F0 males, and reduced thymus weights of both sexes and an increased incidence of stillbirths in the F1 generation. This response is not inconsistent with the result in the screening study with DOTC even though the doses in the 2-generation study were lower than the DOTC study. In the DOTC study, dose-related effects were seen at 10, 100 and 300 mg/kg/day, with post-implantation losses in the top two dose groups. This compares to the absence of such effects in the 2-generation study at the top dose of ~24 mg/kg/day. No teratogenicity was seen in either rat reproduction study; however, dose-related effects on bone formation with resulting severe birth deformations were seen in mice and rabbits. The origin of this interspecies difference is as yet unclear. NOAELs for developmental studies with mixed DOT:MOT esters (78.8:16.9, 80:20) were: 5 mg/kg/day in rats, based on maternal toxicity alone; 45 mg/kg/day in mice, based on the incidence of cleft palate; and 1 mg/kg/day in rabbits, based on the incidence of skeletal head anomalies.

**Environment**

The EPIWIN suite developed by Syracuse Research Corporation has not been validated for chemicals that contain metals in their molecular structure; therefore, there is uncertainty associated with the calculated values and they should be used with caution whenever they are reported below. This could be especially pertinent to estimation of the BCF. This is being investigated in other assessment fora.

DOTC is a solid at room temperature, it melts at 45–47°C, boils at 175°C at 1.3 hPa, has a relative density of 1.15–1.18 g/cm$^3$ at 50°C, and a vapour pressure of $5.16 \times 10^{-6}$ hPa at 25°C. DOT(EHTG)/(IOTG) is a solid at room temperature, it freezes at -90° to -70°C, decomposes at ≥260°C, has a relative density of 1.08 g/cm$^3$ at 20°C, and has an estimated vapour pressure of 0.02 hPa at 25°C.

DOTC and DOT(EHTG/(IOTG) are low to poorly soluble in water with estimated solubilities of 0.3-1.6 mg/L (DOTC) and 1.0 mg/L [DOT(EHTG)/IOTG)]. The inherent chemistry of organotins in water casts doubt on reported water solubility values.

In water, DOTC and DOT(EHTG)/(IOTG) undergo rapid degradation by hydrolysis. Although there is no stability data for DOT(EHTG)/(IOTG), data for DOTC and other organotins [DBTL, and DBT(EHTG)] indicate that the dioctyltin compounds are expected to hydrolyze within minutes to hours in water. It is expected that the chlorines in DOTC will be displaced to form dioctyltin hydroxide which eventually precipitates as the oxide. The thioester ligands on DOT(EHTG)/(IOTG) will be similarly rapidly displaced. It is also possible that the labile ligands can be displaced by other anions in the medium. The displaced thioester ligands, EHTG/IOTG, can also undergo further hydrolysis of the ester linkage to form thioglycolic acid and either ethylhexanol or isooctanol, respectively.

Calculated Log Kows are 5.82 for DOTC and 15.35 for DOT(EHTG)/(IOTG), and log BCFs are 2.8 (DOTC) and 2.0 [DOT(EHTG)/(IOTG)]. These values should be seen with caution (refer to the EPIWIN discussion above).
With Henry's Law constants of $5.35 \times 10^{-8}$ and $1.33 \times 10^{-6}$ atm-m3/mol, respectively, DOT(EHTG) and DOTC would be expected to volatilize from surface water, with volatilization half-lives for a model river or lake of 38 days and 1 year, respectively, for DOTC, and 3 hours and 11 days, respectively, for DOT(EHTG).

If released to the environment, DOTC and DOT(EHTG)/(IOTG) will partition primarily to sediment [45% DOTC, 70% (DOT(EHTG)/(IOTG)]) and soil [38% DOTC, 26% DOT(EHTG)/(IOTG)]. DOTC and DOT (EHTG)/(IOTG) were not readily biodegradable; however, the dioctyltins are atmospherically degraded by photochemically induced hydroxyl radicals [t½ = 6.5 hours for DOTC, 3.9 hours for DOT(EHTG)/(IOTG)].

In the ecotoxicity tests the organisms were most likely exposed to parent substance as well as hydrolysis/degradation products.
For DOTC, the acute aquatic toxicity is as follows: in zebra fish (*B. rerio*) the 96-h $LC_{50}$ > 0.24 mg/L; in *D. magna* the 48-h $EC_{50}$ > 0.28 mg/L; for green algae (*S. subspicatus*) the 72-h $EC_{50}$ for growth rate > 0.002 mg/L and NOEC ≥ 0.002 mg/L.

For DOT(EHTG), the acute aquatic toxicity is as follows: in zebra fish (*B. rerio*) the 96-h $LC_{50}$ > 25 and mg/L; in *D. magna* the 48-h $EC_{50}$ = 0.17 mg/L; for green alga *S. subspicatus* the 72-h $EC_{50}$ for growth rate = 0.17 mg/L and NOEC = 0.04 mg/L.

In 21-day chronic daphnia tests, the toxicity of DOTC is reported as LOEC = 0.87 mg/L and NOEC = 0.41 mg/L, and the toxicity of DOT(EHTG) is reported as $LC/EC_{50}$ (parental survival and reproduction) > 3.2 mg/L, LOEC =1.4 mg/L, and NOEC = 0.29 mg/L.

**Exposure**

DOTC (always manufactured as a mixture with MOTC) is used as an industrial intermediate in the synthesis of organotin chemicals. In 2000, worldwide production of DOTC was estimated at 5,000 to 10,000 metric tonnes. DOT(EHTG) is always manufactured as a mixture with MOT(EHTG) and is added to polyvinyl chloride (PVC) and chlorinated PVC (CPVC) as a heat stabilizer. After being blended into the PVC and CPVC resin, the stabilizers remain there throughout the subsequent processing steps. In 2000, worldwide production of DOT(EHTG) was estimated at 7,500 to 12,500 metric tonnes. Production of DOT(IOTG) has been gradually decreasing over approximately ten years and is being replaced by DOT(EHTG).

The most prominent routes of potential exposure to dioctyltins in an occupational setting are inhalation and dermal contact. Exposure in the workplace is controlled through equipment design, as well as regular air monitoring. Consumer exposure to dioctyltins is primarily from PVC used in potable water pipes, other PVC plastic consumer products, and from PVC used in indirect food packaging applications. Dioctyltin chemicals either leach out of PVC and CPVC articles, or are released into the atmosphere during processing. Releases from production facilities are regulated in many countries. All processing systems are designed and maintained to

ensure that moisture is kept away from the resin compound, since the presence of water creates significant problems during processing. Therefore, losses to water during blending and melt processing are expected to be low, as these are designed to be "dry" processes. Furthermore, water is not used on a regular basis to clean equipment, wash out vessels, etc., and no wastewater is generated. Compounded PVC and CPVC material is solid and any spillage is cleaned up by vacuum or sweeping. Once the PVC or CPVC is melt processed into a final part, the dioctyltin chemicals are held within the resin although leaching may occur.

When tested, PVC water pipes showed an initial release of dioctyltins, which is followed by decreased releases until lower levels of release are reached. All regulatory bodies that have approved of the use of dioctyltins in potable water systems set limits on the amount of tin that can migrate, and in some cases the time over which such migration must fall to a small number. Other articles, such as window profiles and building siding that have dioctyltin stabilizers are expected to show the same type of leaching behavior, i.e., initial level falling to a lower level. Exposure from food packaging also is regulated, with limits on either the amount of migrated dioctyltin or the amount of dioctyltin the food packaging material can contain. Extraction work has shown that levels of dioctyltin extracted from PVC packaging materials by food simulants were below the specific migration limit (SML) established for dioctyltin compounds (0.04 mg/kg as Sn).

Although the above leaching pattern is observed, some studies have found dioctylins in consumer products. In a study of organotins in food in Canada, five of 15 samples of edible oils contained dioctyltin (25.2 to 113 ng/g). Also, a limited number of fruit drinks (3 of 42 samples) contained dioctyltin at 0.9 to 4.3 ng/mL. Dioctyltins have also been found in all indoor dust samples collected from 10 regions from the United Kingdom in 2002, with a mean of 0.130 μg/g. Another study of indoor dust in the United States found an average dioctyltin concentration of 0.11 μg/g (with range of 0.072 to 0.20 μg/g ). Other research did not find dioctyltin in fish or fishery products.

Most PVC and CPVC articles will either be recycled or landfilled at end of life. PVC products are not usually incinerated, but other organotin products that might be incinerated would be destroyed and converted to inorganic tin oxides. Landfill leachate may directly enter the environment Concentration of organotins in leachate samples from sanitary landfills were found to be in the low micrograms per liter range. In addition, it is expected that most leachate would be treated at on-site water treatment facilities or released into a municipal sewer. If landfill leachate should directly enter the environment, there would be dilution of the leachate resulting in lowered environmental concentrations.

**RECOMMENDATIONS AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED**

**Human Health**: The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for human health (skin and eye irritation, dermal sensitization, acute inhalation toxicity, repeated-dose, and reproduction/developmental toxicity). Member countries are invited to perform an exposure assessment for consumers and workers, and if necessary a risk assessment.

**Environment:** The chemicals in this category are candidates for further work. The chemicals possess properties indicating a hazard for the environment (toxicity to fish, aquatic invertebrates and algae). Member countries are invited to perform an exposure assessment for the environment, and if necessary a risk assessment.