*The MAK Collection for Occupational Health and Safety*

# Thiodiethylene bis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]

## MAK Value Documentation – Translation of the German version from 2018

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# Thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] / 2-[2-[3-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)propanoyloxy]-ethylsulfanyl]ethyl 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propanoate

## MAK value documentation

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### Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has evaluated thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] [41484-35-9] to derive a maximum concentration at the workplace (MAK value), considering all toxicological endpoints. Available publications and unpublished study reports are described in detail. Critical effects are hepatic hypertrophy and increased liver weight in male rats in a subchronic feeding study with a NOAEL (no observed adverse effect level) of 12.5 mg/kg body weight and day. As there is no irritating potential, the oral study can be used to derive a MAK value of 2 mg/m³ for the inhalable fraction. As the critical effect is systemic, Peak Limitation Category II is assigned. The default excursion factor of 2 is set as no half-life in blood is known. Classification in Pregnancy Risk Group D is indicated because developmental toxicity studies are lacking. Thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is not genotoxic. Carcinogenicity studies are not available. The substance is not a contact sensitizer in humans and guinea pigs. Skin contact is not expected to contribute significantly to systemic toxicity.



### Keywords

thiodiethylene bis[3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionate]; thiodiethylene bis(3-(3,5-di-tert-butyl-4-hydroxyphenyl)propionic acid ester); 4-hydroxy-3,5-di-tert-butylphenylpropionic acid thioglycolate; thiodi-2,1-ethanediyl bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate); thiodiethyleneglycol-bis(3,5-di-tert-butyl-4-hydroxyhydrocinnamate); 3,5-bis(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid thiodi-2,1-ethanediyl ester; mechanism of action; toxicokinetics; metabolism; (sub)acute toxicity; (sub)chronic toxicity; irritation; allergenic effects; reproductive toxicity; fertility; genotoxicity; peak limitation; prenatal toxicity; germ cell mutagenicity; absorption through the skin; sensitization; occupational exposure; maximum workplace concentration; MAK value; toxicity; hazardous substance



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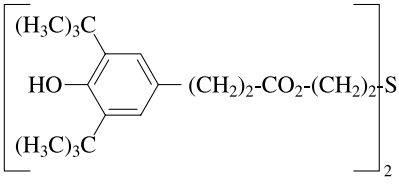
# Thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate]

| | |
|---|---|
| **MAK value (2017)** | **2 mg/m³ I (inhalable fraction)** |
| **Peak limitation (2017)** | **Category II, excursion factor 2** |
| **Absorption through the skin** | **–** |
| **Sensitization** | **–** |
| **Carcinogenicity** | **–** |
| **Prenatal toxicity (2017)** | **Pregnancy Risk Group D** |
| **Germ cell mutagenicity** | **–** |
| **BAT value** | **–** |
| Synonyms | 4-hydroxy-3,5-di-*tert*-butylphenylpropionic acid thioglycolate<br>thiodi-2,1-ethanediyl bis(3,5-di-*tert*-butyl-4-hydroxyhydrocinnamate)<br>thiodiethylene bis(3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionic acid ester)<br>thiodiethyleneglycolbis(3,5-di-*tert*-butyl-4-hydroxyhydrocinnamate) |
| Chemical name | 3,5-bis(1,1-dimethylethyl)-4-hydroxybenzenepropanoic acid thiodi-2,1-ethanediyl ester |
| CAS number | 41484-35-9 |
| Structural formula |  |
| Molecular formula | $C_{38}H_{58}O_6S$ |
| Molar mass | 642.94 g/mol |
| Melting point | 63–71.5 °C (US EPA 2009) |

| | |
|---|---|
| Boiling point | 665 °C (calculated; US EPA 2009) |
| Density | no data |
| Vapour pressure at 25 °C | $10^{-17}$ hPa (calculated; SRC 2016) |
| log $K_{OW}$[1)] | > 10.36 (calculated; US EPA 2009) |
| Solubility | 0.005–0.007 mg/l water, which is practically insoluble in water (US EPA 2009) |
| Stability | EPIWIN could not evaluate the structure, experimental determination not practicable, as not soluble in water (Ciba Specialty Chemicals Corporation 2003, 2007 a) |
| Production | no data |
| Purity | > 98% (US EPA 2009), typical purity of commercial products > 99% (Ciba Specialty Chemicals Corporation 2007 b) |
| Impurities | no data |
| Uses | stabilizer for polyolefins, elastomers and other polymers, additive for synthetic and partially synthetic lubricants for engine oils, ingredient in polymers, resins or adhesives in contact with foodstuffs at concentrations of up to 0.5% (US EPA 2009) |

## 1 Toxic Effects and Mode of Action

After single inhalation, oral and dermal exposure, thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is not toxic even at high doses.

In rabbits, it is not irritating to the skin and the eyes.

The target organ in rats after repeated dietary administration is the liver. In the males, the absolute and relative liver weights were increased and minimal hepatocellular hypertrophy in the centrilobular region was observed after dietary administration for 93 to 103 days at concentrations of 39 mg/kg body weight and day and above. In female rats, these effects did not occur until the dose level of 140 mg/kg body weight and day.

There is no evidence of sensitizing effects of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] in humans. In guinea pigs, experimental skin sensitization studies yielded negative results.

Thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is not mutagenic in bacteria. In the bone marrow cells of Chinese hamsters, it was not clasto-

1) octanol/water partition coefficient

genic up to the high dose of 3500 mg/kg body weight and day after administration by gavage on two days.

There are no studies available for the developmental toxicity and the carcinogenicity of the substance.

## 2 Mechanism of Action

The increase in liver weights and the hepatocellular hypertrophy induced in rats after dietary administration of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] (Ciba-Geigy Limited 1984 a; ECHA 2016) for 90 days indicates increased metabolic activity, namely the induction of metabolizing liver enzymes. This was not investigated further, however.

## 3 Toxicokinetics and Metabolism

There are no data available for the toxicokinetics and the metabolism of the substance.

Absorption of the substance can be concluded from oral studies in which an effect on the liver of rats was found after the administration of 39 mg/kg body weight and day.

The possible ester cleavage of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] produces 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionic acid and the corresponding alcohol. No information on absorption or target organs is available for these two substances.

Experimental data for the absorption of the compound through the skin are not available. Thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is an extremely lipophilic substance with a comparably high molecular weight and extremely poor solubility in water. In substances with a molar mass above 500 Dalton, poor dermal penetration is to be expected (Bos and Meinardi 2000). The log $K_{OW}$ is above 10 and therefore outside the range of validity of the model, so that it is not possible to give any reliable estimation of dermal absorption. From the properties of the compound however, very low absorbability through the skin can be expected, if at all.

## 4 Effects in Humans

Only one study is available for sensitization of the skin.

In a human repeated insult patch test (HRIPT), none of 50 volunteers was sensitized by 15 occlusive applications (10 mg/cm$^2$ over an area of 3 × 3 cm) of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] in powder form (Ciba-Geigy Corporation 1972 a; ECHA 2016).

# 5 Animal Experiments and in vitro Studies

## 5.1 Acute toxicity

### 5.1.1 Inhalation

Studies with single inhalation exposures to thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] are summarized in Table 1.

In three studies with thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] in rats carried out by the contract laboratory Industrial Bio-Test Laboratories (IBT), $LD_{50}$ values of over 3410 mg/m$^3$ for the dust (no other details; Ciba-Geigy Corporation 1975 b; Ciba-Geigy Limited 1976; ECHA 2016) and over 6300 mg/m$^3$ for the vapour (no other details, Ciba-Geigy Corporation 1975 a; ECHA 2016) were obtained. No unusual findings were reported in any of the three studies.

### 5.1.2 Oral administration

The studies of acute toxicity after oral administration are given in Table 2.

Several studies with rats and mice that yielded $LD_{50}$ values of about 5000 mg/kg body weight and above (Ciba-Geigy Corporation 1969, 1972 b, 1975 c; Ciba-Geigy Limited 1971 a, b, 1982 a; ECHA 2016) confirm that thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is practically non-toxic after single oral doses.

One study in rats and one in mice were carried out by the contract laboratory IBT (Ciba-Geigy Corporation 1972 b, 1975 c; ECHA 2016).

### 5.1.3 Dermal application

In two studies carried out by the contract laboratory IBT with male New Zealand White rabbits (300, 1000, 3000 mg/kg body weight; one animal per dose), dermal $LD_{50}$ values of greater than 3000 mg/kg body weight were obtained. Either paste or dry substance in the form of a 3% solution in aqueous methyl cellulose served as initial substance. Both produced pale red erythema on the skin after semi-occlusive application for 24 hours, which was reversible after seven days. No other signs were observed (Ciba-Geigy Corporation 1975 d, e; ECHA 2016).

## 5.2 Subacute, subchronic and chronic toxicity

### 5.2.1 Inhalation

There are no data available.

**Table 1** Studies of the acute toxicity of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] after inhalation exposure

| Species, strain, number/group | Concentration (mg/m³) and exposure conditions | End point | References |
|---|---|---|---|
| rat,<br>not specified,<br>5 ♂ and 5 ♀ | 6300 mg/m³,<br>maximum attainable concentration, however not analysed, 4 hours whole body,<br>vapour,<br>vapour produced by passing clean, dry air through a gas-washing flask filled with undiluted paste,<br>chamber: 80 l, 25 °C, 1013 hPa, air flow: 3.16 l/min | **$LC_{50}$ > 6300 mg/m³**;<br>14-day recovery period: no unusual signs, necropsy yielded no unusual findings | Ciba-Geigy Corporation 1975 a; ECHA 2016 |
| rat,<br>not specified,<br>5 ♂ and 5 ♀ | 3480 mg/m³,<br>maximum attainable concentration, however not analysed,<br>4 hours, whole body,<br>dust,<br>dust produced by passing clean dry air through a rotary disk filled with dry solid,<br>chamber: 80 l, 25 °C, 1020 hPa, air flow: 30 l/min | **$LC_{50}$ > 3480 mg/m³**;<br>14-day recovery period: no unusual signs, necropsy yielded no unusual findings | Ciba-Geigy Corporation 1975 b; ECHA 2016 |
| rat,<br>not specified,<br>5 ♂ and 5 ♀ | 3410 mg/m³,<br>analysed concentration, 4 hours, whole body,<br>dust,<br>dust produced by passing clean dry air through a shaking apparatus filled with dry solid,<br>chamber: 80 l, 24 °C, 1020 hPa, air flow: 13,95 l/min,<br>size distribution of particles (counted): 1–5 µm: 36,8%, 6–10 µm: 38.0%, 11–25 µm: 17.1%; > 25 µm: 8.1% | **$LC_{50}$ > 3410 mg/m³**;<br>14 day recovery period: no unusual signs, necropsy yielded no unusual findings | Ciba-Geigy Limited 1976; ECHA 2016 |

**Table 2** Studies of the acute toxicity of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] after oral administration

| Species, strain, number/group | Dose (mg/kg body weight) | End point | References |
|---|---|---|---|
| **rat** | | | |
| CFE, 5 ♂ and 5 ♀ | 5000 mg/kg body weight, gavage | **$LD_{50}$ > 5000 mg/kg body weight**; somnolence, dyspnoea | Ciba-Geigy Limited 1971 a; ECHA 2016 |
| Sprague Dawley, 1 ♂ | 10, 30, 100, 300, 1000, 3000, 10 000 mg/kg body weight, gavage | **$LD_{50}$ > 10 000 mg/kg body weight**; no unusual signs | Ciba-Geigy Corporation 1975 c; ECHA 2016 |
| Tif:RAIf, 5 ♂ and 5 ♀ | 5000 mg/kg body weight, gavage | **$LD_{50}$ > 5000 mg/kg body weight**; dyspnoea, exophthalmus, ruffled fur, curved body position | Ciba-Geigy Limited 1982 a; ECHA 2016 |
| **mouse** | | | |
| $CF_1S$, 10 ♂ | 0, 1250, 2500, 5000 mg/kg body weight, gavage | **$LD_{50}$ > 5000 mg/kg body weight**; **1250 mg/kg body weight and above**: reduced motor activity, lateral extension of hind limbs, ataxia, muscular weakness, increased lacrimation; **2500 mg/kg body weight and above**: body weights slightly ↓; **5000 mg/kg body weight**: mortality: 1/10, in dead animal: congested lungs, small amount of blood in the lumen of the gastrointestinal tract | Ciba-Geigy Corporation 1969; ECHA 2016 |
| HA (ICR), 5 ♂ and 5 ♀ | 3038, 4556, 6834, 10 250 mg/kg body weight, gavage | **$LD_{50}$: 4556 mg/kg body weight**; **3038 mg/kg body weight and above**: hypoactivity, muscular weakness, laboured breathing; **4556 mg/kg body weight and above**: tremor, prostration; **6834 mg/kg body weight and above**: spasms; in dead animals: enteritis, haemorrhage in the gastrointestinal tract | Ciba-Geigy Corporation 1972 b; ECHA 2016 |
| Swiss-ICR, 5 ♂ and 5 ♀ | 5000 mg/kg body weight, gavage | **$LD_{50}$ > 5000 mg/kg body weight**; somnolence, dyspnoea, ruffled fur | Ciba-Geigy Limited 1971 b; ECHA 2016 |

### 5.2.2 Oral administration

The studies of repeated oral administration are summarized in Table 3.

In a range-finding study with dietary administration for 28 days in male and female Tif:RAIf rats, the absolute and relative liver weights were increased by at least 30% in the males even at the low dose of 96 mg/kg body weight and day (Ciba-Geigy Limited 1982 b; ECHA 2016).

In a study carried out according to OECD Test Guideline 408 with Tif:RAIf rats with dietary administration for 93 to 103 days, increased relative liver weights were observed in the male rats at the low dose of 4.4 mg/kg body weight and day and above. In male rats given 39 mg/kg body weight and day and above, minimal hepatocellular hypertrophy in the centrilobular region was seen. The females were found to be less sensitive. Increased absolute testis weights were determined in the males at 12.5 mg/kg body weight and day and above, which were, however, not dose-dependent. The increase was about 10% in each case. Moreover, there was no statistically significant change in the relative testis weights (Ciba-Geigy Limited 1984 a; ECHA 2016). As only the absolute and not the relative testis weights were increased and no histopathological changes were observed in this organ, no toxicological relevance is attributed to this finding (see Section 5.5.1). An increase in absolute and relative liver weights by less than 20% without histological changes in this organ is not considered adverse. Based on the increased absolute and relative liver weights and the minimal hepatocellular hypertrophy, the NOAEL (no observed adverse effect level) for liver toxicity was 12.5 mg/kg body weight in the male rats and 40 mg/kg body weight and day in the females.

Two studies with rats and one with dogs were carried out by the contract laboratory IBT in 1973 (Ciba-Geigy Corporation 1973 a, b, c; ECHA 2016). In studies carried out by the IBT at that time, irregularities in the conduct of the study and the documentation of the results were found. Studies with repeated administration were those most affected (OECD 2005). As the quality of these studies cannot be evaluated due to such irregularities, the results cannot be included in the evaluation. In the study with dogs, due to the consistency with the target organs found in the rat studies, the results could at best be taken as an indication that the liver is also the target organ in dogs.

### 5.2.3 Dermal application

There are no data available.

**Table 3** Effects of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] after repeated oral administration

| Species, strain, number/group | Exposure | Findings | References |
|---|---|---|---|
| **rat**, Tif:RAIf, 10 ♂, 10 ♀ | **28 days**, range-finding study, 0, 1000, 3000, 10 000 mg/kg feed, ♂: 0, 96, 285, 1042 mg/kg body weight and day, ♀: 0, 88, 271, 941 mg/kg body weight and day, purity: > 99% | **no NOAEL**;<br><br>**96/88 mg/kg body weight and above**:<br>♂: liver: absolute and relative weights ↑ (96, 285, 1042 mg/kg body weight: absolute: 34%, 29%, 40%; relative: 30%, 34%, 39%);<br><br>**285/271 mg/kg body weight and above**:<br>♂: body weight gains slightly ↓;<br>♀: food consumption slightly ↓; thyroid gland: absolute and relative weights ↓;<br><br>**1042/941 mg/kg body weight**:<br>♂: thyroid gland: absolute and relative weights ↓; thymus: absolute weights and weights in relation to that of brain ↓;<br><br>general: no treatment-related mortality; no unusual findings in ophthalmoscopic examinations and hearing tests, haematology, clinico-chemical parameters in the blood, gross-pathological examination of organs;<br><br>no histopathological examination carried out | Ciba-Geigy Limited 1982 b; ECHA 2016 |

**Table 3** (continued)

| Species, strain, number/group | Exposure | Findings | References |
|---|---|---|---|
| **rat**, Tif:RAIf, 20 ♂, 20 ♀ | **93–103 days**, 0, 60, 200, 600, 2000 mg/kg feed, ♂: 0, 4.4, 12.5, 39, 138 mg/kg body weight and day, ♀: 0, 4.5, 13, 40, 140 mg/kg body weight and day, purity: > 99%, OECD Test Guideline 408 | **4.4/4.5 mg/kg body weight and above**:<br>♂: liver: relative weights ↑ (4.4, 12.5, 39, 138 mg/kg body weight: 12%, 19%, 26%, 34%);<br>**12.5 mg/kg body weight**: ♂: **NOAEL for liver toxicity** (see text);<br>**12.5/13 mg/kg body weight and above**:<br>♂: liver: absolute weights ↑ (12.5, 39, 138 mg/kg body weight: 19%, 29%, 37%);<br>gonads: absolute weights ↑ (12.5, 39, 138 mg/kg body weight: 11%, 11%, 14%; no statistically significant change in relative weights);<br>**40 mg/kg body weight**: ♀: **NOAEL for liver toxicity**;<br>**39/40 mg/kg body weight**:<br>♂: liver: minimal hepatocellular hypertrophy in centrilobular region (39, 138 mg/kg body weight: 6/20, 20/20); kidneys: absolute weights ↑ (39, 138 mg/kg body weight: 7%, 10%, no statistically significant change in relative weights);<br>♀: liver: relative weights ↑ (40, 140 mg/kg body weight: 7%, 19%);<br>**138/140 mg/kg body weight**:<br>♀: liver: absolute weights ↑ (15%), minimal hepatocellular hypertrophy in centrilobular region (3/19);<br>general: no deaths; no unusual findings in: ophthalmoscopic examinations and hearing tests, haematology, clinico-chemical parameters in the blood, gross-pathological examination of the organs | Ciba-Geigy Limited 1984 a; ECHA 2016 |

**Table 3** (continued)

| Species, strain, number/group | Exposure | Findings | References |
|---|---|---|---|
| **rat**, albino (no other details), 5 ♂, 5 ♀ | **6 weeks**, 0, 2.5% in the feed, ♂: about 0, 1630 mg/kg body weight and day; ♀: about 0, 1880 mg/kg body weight and day (using the data given for body weights and for weekly food consumption), purity: not specified; contract laboratory IBT | **about 1630/1880 mg/kg body weight**: ♀: body weight gains and food consumption ↓;<br>general: no deaths; no unusual changes in: body weights, clinical signs, haematology, clinico-chemical parameters in the blood, gross-pathological examination of 8 organs;<br>no histopathological examination carried out, no organ weights determined;<br>not suitable for the evaluation, as irregularities in the conduct of the study and documentation were found in the investigating laboratory | Ciba-Geigy Corporation 1973 a; ECHA 2016 |
| **rat**, albino (no other details), 15 ♂, 15 ♀ | **90 days**, 0, 10 000, 20 000, 30 000 mg/kg diet, ♂: about 0, 719, 1423, 2197 mg/kg body weight and day; ♀: about 0, 765, 1677, 2485 mg/kg body weight and day (using the data given for body weights and for weekly food consumption), purity: not specified; contract laboratory IBT | **about 719/765 mg/kg body weight and above**: liver: absolute and relative weights ↑ (by up to about 30%, not dose-dependent);<br>general: no treatment-related mortality; no unusual changes in: body weights, body weight gains, food consumption, clinical signs, haematology, clinico-chemical parameters in the blood, urinalysis, gross-pathological examination, microscopic examination of about 34 organs/tissues;<br>not suitable for the evaluation, as irregularities in conduct and documentation were found in the investigating laboratory | Ciba-Geigy Corporation 1973 b; ECHA 2016 |

**Table 3** (continued)

| Species, strain, number/group | Exposure | Findings | References |
|---|---|---|---|
| **dog**, beagle, 4 ♂, 4 ♀ | **90 days**, 0, 10 000, 20 000, 30 000 mg/kg diet, ♂: about 0, 391, 760, 1271 mg/kg body weight and day, ♀: about 0, 371, 786, 1200 mg/kg body weight and day (using the data given for weekly food consumption related to body weight), purity: not specified; contract laboratory IBT | **about 391/371 mg/kg body weight and above**: liver: absolute and relative weights ↑ (♂, ♀: > 30%);<br>**about 760/786 mg/kg body weight**: ♀: serum: alkaline phosphatase ↑;<br>general: no deaths; no unusual changes in: body weights, body weight gains, food consumption, clinical signs, urinalysis, haematology, gross and histopathological examination of about 26 organs/tissues;<br>not suitable for the evaluation, as irregularities in the conduct of the study and documentation were found in the investigating laboratory;<br>due to consistency with the target organ in rats, this study could be taken as an indication that the liver is also the target organ in dogs | Ciba-Geigy Corporation 1973 c; ECHA 2016 |

IBT: Industrial Bio-Test Laboratories; NOAEL: no observed adverse effect level

## 5.3 Local effects on skin and mucous membranes

### 5.3.1 Skin

In a study carried out by the contract laboratory IBT, 0.5 g moistened thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] in powder form was applied occlusively to the shaved dorsal skin of 4 New Zealand White rabbits for 24 hours. The skin was examined after 24 and 72 hours. Evaluation of the abraded and intact skin according to the Draize method yielded an average primary irritation value of 0. The substance was therefore not found to be irritating to the rabbit skin (Ciba-Geigy Corporation 1971; ECHA 2016). The results of the study do not contradict those obtained from the studies of eye irritation, and are therefore included.

### 5.3.2 Eyes

An eye irritation test was carried out in 3 male and 3 female Himalayan rabbits in accordance with the Test Guidelines of the US Association of Food and Drug Officials (US AFDO 1959), which are similar to OECD Test Guideline 405. In this test, 0.1 g thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] was instilled into the conjunctival sac of one eye of each rabbit, and the lid was held closed for one second. The other eye was not treated and was used as a control. In 3 of the 6 animals, the treated eye was rinsed with 10 ml water about 30 seconds after the instillation, and examined after 1, 2, 3, 4 and 7 days. At all examination times the irritation scores were 0, irrespective of whether the eyes were rinsed or not (Ciba-Geigy Limited 1975; ECHA 2016). The substance was therefore regarded as not irritating to the eyes of rabbits.

In two studies carried out according to the Draize method by the contract laboratory IBT, 100 mg thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] was introduced as an undiluted dry substance in one study and as a paste in the second study into the right eye of 3 New Zealand White rabbits (no other details). An irritation score of 6.7 of a maximum 110 was obtained with the dry substance. The changes observed had already returned to normal after 48 hours (Ciba-Geigy Corporation 1975 f; ECHA 2016). An irritation score of 24.4 of a maximum 110 was obtained with the paste. All changes had regressed after seven days (Ciba-Geigy Corporation 1975 g; ECHA 2016).

## 5.4 Allergenic effects

### 5.4.1 Sensitizing effects on the skin

In a maximization test with 10 female and 10 male Pirbright White guinea pigs, intradermal induction was carried out using 5% of the test substance (purity > 95%) in arachis oil, and the topical induction and challenge treatment were performed with 50% preparations in petrolatum. In a range-finding study, the test substance had no irritant effects up to a concentration of 50%, so that non-occlusive pretreatment with a 10% preparation of dodecylsulfate in petrolatum was carried out 24 hours prior to the topical induction. At the challenge, none of the animals produced a reaction (Ciba-Geigy Limited 1993; ECHA 2016).

### 5.4.2 Sensitizing effects on the airways

There are no data available.

## 5.5 Reproductive and developmental toxicity

### 5.5.1 Fertility

There are no fertility studies available.

In the feeding study with Tif:RAIf rats carried out according to OECD Test Guideline 408 (see Section 5.2.2) for 93 to 103 days, the absolute testis weights were increased in male animals after thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] doses of 12.5 mg/kg body weight and day and above. This increase was not dose-dependent, and the increase was about 10% in each case. Moreover, there was no statistically significant change in the relative testis weights. No treatment-related gross or histopathological changes in the male and female reproductive organs were found up to the highest dose tested of 138 mg/kg body weight and day for the male rats and 140 mg/kg body weight and day for the females (Ciba-Geigy Limited 1984 a; ECHA 2016). As only the absolute and not the relative testis weights were increased and no histopathological changes were found in this organ, no toxicological relevance is attributed to this finding. As, up to the highest dose tested, no histopathological changes in the male and the female reproductive organs occurred, the NOAEL for effects on the male and the female reproductive organs is the highest dose tested of 140 mg/kg body weight and day.

### 5.5.2 Developmental toxicity

There are no data available.

## 5.6 Genotoxicity

### 5.6.1 In vitro

In a bacterial mutagenicity test (plate incorporation), similar to OECD Test Guideline 471, thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] (purity: commercial grade), dissolved in acetone, was tested at concentrations of 0, 20, 80, 320, 1280 and 5120 µg/plate in the Salmonella typhimurium strains TA98, TA100, TA1535 and TA1537. The positive controls confirmed the validity of the test system. The test substance precipitated at concentrations of 320 µg/plate and above. There was no cytotoxicity up to the highest concentration tested. The substance was not mutagenic in bacteria (Ciba-Geigy Limited 1984 b; ECHA 2016).

### 5.6.2 In vivo

In a nucleus anomaly test, 3 male and 3 female Chinese hamsters were given gavage doses of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] of 0, 875, 1750 or 3500 mg/kg body weight and day dissolved in 0.5% aqueous sodium

carboxymethylcellulose solution on 2 consecutive days. The animals were killed 24 hours after the final treatment, and the bone marrow was examined. The solvent was used as a negative control, and cyclophosphamide (128 mg/kg body weight) served as a positive control. In the treated animals, the percentage of cells with nuclear anomalies in all dose groups was within the range of the control animals. The percentage of cells with nuclear anomalies in the solvent control group was 0.5% (only few Jolly bodies = micronuclei) and in the positive control group 12.5% (a few Jolly bodies, fragments of nuclei in erythrocytes, micronuclei in erythroblasts, micronuclei in leukopoietic cells = precursor cells) (Ciba-Geigy Limited 1984 c; ECHA 2016). In this test, thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionate] was not clastogenic. No information is available for the ratio between polychromatic and normochromatic erythrocytes (PCE/NCE). For this reason, it is questionable whether the test substance reached the bone marrow.

### 5.7 Carcinogenicity

There are no data available.

### 5.8 Other effects

Studies in yeast cells using the test systems Yeast Estrogenic Screening (YES) and Yeast Androgenic Screening (YAS) did not reveal oestrogenic or antioestrogenic effects or androgenic or antiandrogenic effects at thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] concentrations of up to 0.1 mmol/l (BASF 2013 a, b).

## 6 Manifesto (MAK value/classification)

The critical effects of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] are hepatocellular hypertrophy and increased liver weights in male rats after dietary administration of the substance for 93 to 103 days.

**MAK value.** Studies with humans or inhalation studies with animals are not available.

In a study carried out according to OECD Test Guideline 408, in which Tif:RAIf rats were given the substance with the diet for 93 to 103 days, the absolute and relative liver weights in the males were increased by more than 20% at concentrations of 39 mg/kg body weight and day and above. These increases correlated with minimal hepatocellular hypertrophy in the centrilobular region. These findings were regarded as adverse effects. The female rats were found to be less sensitive (Ciba-Geigy Limited 1984 a; ECHA 2016). The NOAEL for liver toxicity was 12.5 mg/kg body weight and day in the males and 40 mg/kg body weight and day in the females. The systemic effects show that absorption takes place despite the poor solubility of the substance in water. The substance is therefore not inert, which means that the general threshold limit value for dust is not applicable. Data for the toxicokinetics of the substance are not available. Structurally, methyl-3-(3,5-di-*tert*-butyl-4-hydroxy-

phenyl)propionate corresponds to half of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] without the $CH_2$ chain and the sulfur. In rats, after single oral doses of $^{14}$C-methyl-3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate of 10 mg/kg body weight, about 40% is eliminated with the urine (OECD 2001), which indicates that oral absorption is at least 40%. For thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate], oral absorption of 40% is likewise assumed. The following toxicokinetic data are taken into consideration for the extrapolation of the NOAEL of 12.5 mg/kg body weight and day to a concentration in workplace air: the daily exposure of the animals in comparison with the 5 days per week exposure at the workplace (7:5), the corresponding species-specific correction value (1:4) for the rat, the assumed oral absorption (40%), the body weight (70 kg) and respiratory volume (10 m$^3$) of the person, and the assumed 100% absorption by inhalation. The concentration calculated from this is 12 mg/m$^3$. Using the standard procedure of the Commission for the extrapolation of the data from the experimental animal study to humans (1:2) (see List of MAK and BAT Values, Section I), the assumed increase in effects over time (1:2) and the preferred value approach, a threshold limit value of 2 mg/m$^3$ I (inhalable fraction) is derived. This value is based on the systemic effects only. Inhalation studies are not available. A possible effect in the respiratory tract due to the possible local formation of 3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionic acid resulting from ester cleavage of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is not taken into consideration. However, the MAK values for organic acids are higher than 2 mg/m$^3$ (for example, acetic acid: 25 mg/m$^3$, propionic acid: 31 mg/m$^3$). The MAK value of 2 mg/m$^3$ therefore covers possible effects of the acid. Another ester, dicarboxylic acid dimethylester, has a MAK value of 5 mg/m$^3$. This argument is supported also by the fact that the hydrolytic cleavage of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is, due to its poor solubility in water, presumably very slow.

**Peak limitation.** As the MAK value of thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] has been derived from systemic effects, the substance is assigned to Peak Limitation Category II. No specific data for its half-life in blood are available. The default excursion factor of 2 has therefore been set.

**Prenatal toxicity.** No developmental toxicity studies have been carried out. As data for prenatal toxicity are not available, the substance is assigned to Pregnancy Risk Group D.

**Carcinogenicity.** Carcinogenicity studies are not available. Thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] was not mutagenic in bacteria and not clastogenic in the bone marrow cells of Chinese hamsters, however without proof that the target cells were exposed. From the available data, the substance is not suspected to be carcinogenic. The substance is therefore not classified in one of the categories for carcinogens.

**Germ cell mutagenicity.** Thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] was not mutagenic in bacteria. In a nucleus anomaly test with male and female Chinese hamsters, the substance was not clastogenic in the bone marrow up to the highest dose tested of 3500 mg/kg body weight and day administered two times by gavage. It is, however, unclear whether the target cells were

exposed to the test substance. The structure of the substance, however, does not suggest that it is mutagenic. The substance is therefore not classified in one of the categories for germ cell mutagens.

**Absorption through the skin.** With dermal $LD_{50}$ values of greater than 3000 mg/kg body weight without the presence of any irritation, thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is of very low acute dermal toxicity. Experimental data for its dermal absorption are not available. Reliable model calculations on the basis of physico-chemical properties are not possible for this substance. However, due to the physico-chemical properties of the compound, significant dermal absorption and consequently a relevant contribution to systemic toxicity are not to be expected. Therefore, thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-propionate] is not designated with an "H" (for substances which can be absorbed through the skin in toxicologically relevant amounts).

**Sensitization.** There are no clinical or positive experimental findings of skin or airway sensitization caused by thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate]. Therefore, thiodiethylene bis[3-(3,5-di-*tert*-butyl-4-hydroxyphenyl)propionate] is designated neither with "Sh" (for substances which cause sensitization of the skin) nor with "Sa" (for substances which cause sensitization of the airways).

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