6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol

(CAS No: 96-69-5)

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

1   Introduction

The present document contains the assessment of the health hazard of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by MA Maclaine Pont, M.Sc. (Wageningen University and Research Centre, Wageningen, the Netherlands).

The evaluation of the toxicity of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol has been based on the review by the American Conference of Governmental Industrial Hygienists (ACG92). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, in November 1999, literature was searched in the databases Toxline, Medline, and Chemical Abstracts starting from 1981, 1966, and 1937, respectively, and using the following key words: Lowinox; Santonox; Yoshinox; Disperse MB-61; phenol, 4,4'-thiobis(2-(1,1-dimethylethyl)-5-methyl-; m-cresol, 4,4'-thiobis(6-tert-butyl)-; m-cresol, thiobis (6-tert-butyl)-; and 96-69-5.
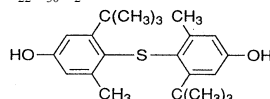
In July 2000, the President of the Health Council released a draft of the document for public review. Comments were received from the following individuals and organisations: P Dollenmeier (Ciba Speciality Chemicals Inc., Basel, Switzerland). These comments were taken into account in deciding on a revised version of the document.

An additional literature search was performed in Toxline and Medline in October 2004.

In December 2004, the President of the Health Council released a revised draft of the document for public review. No comments were received.

2   Identity

name   : 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol
synonyms   : 4,4'-thiobis(6-*tert*-butyl-*m*-cresol); bis(3-*tert*-butyl-4-hydroxy-6-
                          methylphenyl) sulfide; bis(4-hydroxy-5-*tert*-butyl-2-methylphenyl)
                          sulfide; phenol, 4,4'-thiobis(2-(1,1-dimethylethyl)-5-methyl-; 4,4'-
                          thiobis(2-*tert*-butyl-5-methylphenol); 4,4'-thiobis(6-*tert*-butyl-3-
                          methylphenol); 4,4'-thiobis(3-methyl-6-*tert*-butylphenol); 1,1'-
                          thiobis(2-methyl-4-hydroxy-5-*tert*-butylbenzene
CAS number   : 96-69-5
molecular formula   : $C_{22}H_{30}O_2S$
structural formula   :

3   Physical and chemical properties

molecular weight   : 358.5
melting point   : 150ºC
boiling point   : -
flash point   : -
vapour pressure   : -
solubility in water   : slightly soluble (8 g/100 mL)
log $P_{octanol/water}$: 8.24 (estimated)
conversion factors   : not applicable
Data from ACG92, http://www.syrres.com/esc/est_kowdemo.htm.

6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol is a light grey to tan powder. It has a slightly aromatic odour (ACG92).

4   Uses

6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol is used as an antioxidant in high- and low-pressure polyethylenes and polypropylenes, neoprene, and other synthetic rubbers (ACG92).

5   Biotransformation and kinetics

After oral administration of ^{14}C-labelled 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol to male F344/N rats, the compound was incompletely absorbed, although the rate of absorption was proportional to the dose, once the compound reached the small

intestine. Intravenous administration resulted in more of the compound being retained in the tissues and less being excreted than was observed following oral treatment. Three days after a single oral dose of 5, 50, or 500 mg/kg bw or after a single intravenous injection of 5 mg/kg bw, none of the tissues contained more than 4% of the total dose. After administration (both oral and intravenous), 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol was rapidly distributed throughout the body with the liver being the major tissue depot. Significant amounts of the compound were also present in blood, muscle, skin, and adipose tissue. 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol was initially rapidly cleared from all tissues except from adipose tissue, while a small percentage of the total dose tended to persist in liver and skin. The initial rapid clearance from adipose tissue, liver, and skin was followed by a slow second phase of clearance of radioactivity, which consisted mainly of parent compound. This suggested that repeated exposure to 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol might result in accumulation of parent compound in the liver and lipid-rich tissues. 6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol-derived radioactivity was primarily excreted via the bile into the faeces, more than half of it within the first day. The total amount of radioactivity in the bile was due to metabolites of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol, but metabolites accounted for only 80% of the radioactivity in the faeces. According to Birnbaum et al., this suggested that the metabolite(s) might have been subjected to hydrolysis by the intestinal microflora. Released parent compound would then either be reabsorbed, resulting in prolongation of the whole body half-life, or excreted, accounting for the appearance of apparently unchanged parent compound in the faeces. The clearance of radioactivity from the faeces occurred with a half-life of 20 h, similar to the transit time of materials through the gastrointestinal tract. Less than 2% of the radioactivity administered, all consisting of metabolites, was excreted into the urine. The majority of urinary excretion occurred within the first day with a clearance half-life of 9 h. The major metabolites appeared to be glucuronide conjugates of the parent compound (Bir83).

In a subsequent experiment, Birnbaum and Heany administered ^{14}C-labelled 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol intravenously, orally, and dermally to female Sencar mice and dermally to male F344/N rats. They compared the faecal excretion in rats and mice after different routes of exposure, using the rat data from the previous study as well (Bir87). The results are presented in Table 1.

Table 1 Effect of route of exposure on faecal elimination and skin retention of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol-derived radioactivity in Sencar mice and Fischer rats (Bir87).

species	exposure route (dose in mg/kg bw)	% IBB[a] in daily faecal excretions			% IBB in total faecal excretions	% IBB on treated skin site
		day 1	day 2	day 3		
mouse	intravenous (5)	59	18	17	94	
	oral (5)	89*	6.5	2*	96	
	dermal (5)	5**	9	8	22**	76
rat	intravenous (5)	-	-	-	77[b]	
	oral (5)	-	-	-	103[b]	
	dermal (5)	-	-	-	1.7***	98
	dermal (50)	-	-	-	0.3	100
	dermal (200)	-	-	-	0.4	100

* p<0.05 vs. intravenous treatment; ** p<0.01 vs. oral or intravenous treatment; *** p<0.05 vs. doses of 50 or 200 mg/kg bw.

[a]   IBB = internal body burden, i.e., the total accountable radioactivity representing the sum of the radioactivity in the excreta, skin site, and carcass. It averaged 93% of the applied dose.

[b]   Data from Bir83.

In agreement with Birnbaum and Heaney, the committee concludes that mouse skin is more permeable to 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol than rat skin. Absorption did not increase linearly as the dose increased. The disposition of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol after oral and intravenous administration was similar in rats and mice, and the faeces is the major route of elimination in both species.

6   Effects and mechanism of action

Human data

Two cases were described of persons who developed dermatitis after wearing latex gloves. They reacted positively to a patch test with a 1% solution of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol in petrolatum. On the other hand, 65 patients, 37 women and 28 men, were examined to a 2% solution in petrolatum, and none had a positive allergic reaction (Ric91).

Animal data

Irritation and sensitisation

The committee did not find data from experimental animal studies on the potential irritation and sensitisation of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol.

Acute toxicity

The approximate lethal oral dose of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol in rats was 5000 mg/kg bw, with gastroenteritis being the chief sign of intoxication (ACG92). Oral LD_{50} values of 2345 and 6900 mg/kg bw for rats and of 3200 mg/kg bw for rabbits have been published (Bir87, NIO04). The dermal LD_{50} in rabbits was >1260 mg/kg bw (Bir87). The intraperitoneal LD_{50} in mice was 50 mg/kg bw (NIO04).

Repeated-dose toxicity

As part of a immunotoxicological evaluation of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol (see also Section 'Immunotoxicity' and Table 3), toxicological end points (investigated in 3-16 animals/group), including body and organ weights, histology, haematology, serum chemistry, bone marrow cellularity, hepatic microsomal parameters, were evaluated in female $B6C3F_1$ mice (n=52-56/group) given oral (gavage) doses (vehicle: corn oil) of 0, 10, 100, and 200 mg/kg bw for 14 days. During exposure, no mortality or signs of toxicity were observed. Body weights of the animals of the mid- and high-dose groups were statistically significantly increased at treatment day 8 and 15. In the animals sacrificed for macroscopic and microscopic evaluation (n=8/group), body weights were statistically significantly increased at the mid and high dose. There were increases in absolute and relative spleen weights, being statistically significant at all doses, and in absolute and relative liver weights reaching statistically significance at the mid and high dose and at the high dose, respectively, and a statistically significant decrease in relative kidney weights at the high dose; the weights of other organs (e.g., the thymus, lungs, adrenal glands) were not affected. The weight changes in the spleen and kidneys were not accompanied by histological changes in any of the treated groups when compared to controls. The livers of the high-dose animals showed mild focal hydropic degeneration (hepatocytes adjacent to central veins), mild hepatitis (small focal collections of acute and chronic inflammatory cells), occasional degeneration and regeneration

(mitotic figures) of hepatocytes, and a slight increased number of Kupffer cells. Apart from a significant (p<0.01) increase in bilirubin at the high dose, serum chemistry values (alanine aminotransferase, albumin, blood urea nitrogen, glucose, total protein) were not affected when compared to those of controls (examined in 8 animals/group). Investigation of glutathione and microsomal parameters (in 6 animals/group) revealed increased levels of microsomal protein (at the mid - not significant - and high dose - p<0.01), of cytochrome P450 (at the mid - p<0.05 - and high dose - p<0.01), of aminopyrine demethylase and of aniline hydroxylase (both at the mid - p<0.01 - and high dose - p<0.01), while glutathione and arylhydrocarbon hydroxylase levels were not changed. [The committee notes that in this subset of animals, there was a dose-dependent increase in absolute liver weights being statistically significant (p<0.01) at all dose levels (relative weights were not given)]. There were no marked effects on haematology values (investigated in 4-8 animals/group) except for increases in the number of reticulocytes and of leukocytes at the mid (p<0.01 and not significant, respectively) and high dose (p<0.01 for both). Absolute differential counts indicated significant increases in the number of lymphocytes and neutrophils at the high dose, while bone marrow analyses, performed in 6 animals of this group, showed increases in the number of cells/femur (by 30%, p<0.01), of macrophage progenitors/femur (by 28%, p<0.01), and of granulocyte-monocyte progenitors/femur (by 20%, not significant) (Mun88).

NTP performed 15-day, 13-week, and 2-year feed studies in male and female F344/N rats and B6C3F$_1$ mice.

In the 15-day studies, groups of 10 rats/sex were fed diets containing 0, 1000, 2500, 5000, 10,000, or 25,000 ppm 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol, resulting in doses of ca. 95, 235, 335, or 365 mg/kg bw/day for males and of 85, 220, 325, or 270 mg/kg bw/day for females. Due to early deaths, the approximate doses for the 25,000-ppm group could not be calculated. None of the rats of 25,000-ppm group survived, all dying in the second treatment week. In the 10,000-ppm group, mortality occurred in 3/10 males (at days 11 and 14) and 4/10 females (at days 12, 13, and 15). Surviving animals had significant mean weight losses (by 27-29%) and decreased mean final body weights (by 43-51%), which was accompanied by decreased feed consumption (by roughly 60-80%) due to poor feed palatability. Clinical signs observed in these animals included diarrhoea midway or late into the study. Post-mortem examinations showed significant increases in leukocyte counts in females and in segmented neutrophil counts in males and females. This increase was not accompanied by an increase in immature forms, suggesting, according to NTP, that this was not due to an inflammatory response but rather to a shift in the total blood pool distribution

without an absolute increase. Effects observed on reticulocytes and erythrocytes, lymphocyte depletion in the thymus and spleen, and depletion of haematopoietic cells from the bone marrow were thought to be related to the debilitation and stress, rather than to primary effects on, for instance, the bone marrow. All absolute and relative organ weights determined were significantly decreased. Microscopic examination revealed mainly kidney (renal tubular necrosis) and glandular stomach (congestion, haemorrhage) lesions. In the 5000-ppm group, all animals survived treatment. Mean final body weights and mean body weight gains were significantly decreased in males (by 22 and 71%, respectively) and females (by 18 and 77%, respectively), which was accompanied by decreased feed consumption (by roughly 30-40%). Animals had diarrhoea starting in the second part of the study. Post-mortem, there were effects on leukocytes, neutrophils, reticulocytes, and erythrocytes similar to those seen in the 10,000-ppm group. There were statistically significant changes in relative organ weights of the heart (males: decrease), liver (males, females: increase), and thymus (males: decrease) but not in the incidences of microscopic lesions. In the 2500- and 1000-ppm group, no significant effects were seen, apart from increased relative liver weights in males at 2500 ppm and in the leukocyte numbers in females at both levels (NTP94).

Groups of 10 mice/sex were similarly treated. Administration of 1000, 2500, or 5000 ppm resulted in daily doses of ca. 285, 585, or 475 mg/kg bw for males and of 360, 950, or 1030 mg/kg bw for females. Since all animals of the 10,000- and 25,000-ppm group died (between day 8 and 12 (males) and 6 and 8 (females) and day 4 and 6, respectively), approximate doses could not be calculated. In the 5,000-ppm group, mortality amounted to 8/10 animals of each sex (days of death: 9-15). In the 2500-ppm group, all animals survived. Mean body weights and body weight gains of males were similar to those of controls; in females, they were lower by 13 and 90%, respectively. No clinical signs of toxicity were observed. Post-mortem, segmented neutrophilic counts were affected similarly to rats. Organ weight changes included decreased relative heart, kidney, and lung weights in males and decreased relative kidney and increased relative liver weights in females. There were no microscopic findings. In the animals given 1000 ppm, only decreases in relative heart and kidney weights in males were observed (NTP94).

In the subsequent 13-week study, rats (n=10/sex/group) were fed 0, 250, 500, 1000, 2500, and 5000 ppm resulting in doses of ca. 15, 30, 60, 165, and 315 mg/kg bw for males and of 15, 35, 70, 170, and 325 mg/kg bw for females. In the 5000-ppm group, mean final body weights and mean body weight gains were significantly decreased in male (by ca. 40 and 60%, respectively) and female

animals (by ca. 30 and 50%, respectively), which was accompanied by decreased feed consumption (of ca. 20-40% in males and ca. 15-25% in females). The major clinical finding was diarrhoea appearing at about day 60. Haematology and clinical chemistry analyses performed on blood sampled 2 days before the end and at the end of the experiment, respectively, showed increases in serum levels of alkaline phosphatase in males ($p \leq 0.01$) and females (not significant) and of alanine aminotransferase ($p \leq 0.01$ in both sexes), in total leukocyte counts in males (not significant) and females ($p \leq 0.01$), in segmented neutrophil counts in males ($p < 0.01$) and females ($p \leq 0.05$), in band neutrophil counts in females ($p \leq 0.01$), in lymphocyte counts in females (not significant), and in atypical lymphocyte counts in females ($p \leq 0.01$) and statistically significantly decreases in haematocrit, haemoglobin, and mean erythrocyte volume values in males and in mean erythrocyte values in females. Relative organ weight changes included increases in kidney, liver, and spleen weights in males and females and decreases in thymus weights in males. Histologically, liver (mild bile duct hyperplasia, moderate to marked Kupffer cell hypertrophy, minimal necrosis), kidney (minimal to mild necrosis, minimal pigmentation), and mesenteric lymph nodes (moderately increased size and number of macrophages) lesions were seen in 9-10 animals/sex. In the 2500-ppm group, there was no effect on body weight (gain). Results of 3 neurotoxicity trials (forelimb and hind limb grip strength, tail flick, startle response, foot splay), performed during the last 8 exposure days in this and the 1000-ppm group only, showed a significant increase in forelimb and hind limb grip strength in both sexes. Changes in haematology and clinical chemistry values included statistically significant increases in serum levels of alkaline phosphatase in males and females and of alanine aminotransferase in males and females and in band neutrophil counts in females and decreases in haematocrit, haemoglobin, and mean erythrocyte volume values in males. Changes in relative organ weights were limited to the liver (increase) and thymus (decrease) of males. Upon microscopic examination, there were similar lesions (no kidney necrosis) as seen at 5,000 ppm but generally less severe (i.e., minimal or minimal to mild) and a lower incidence (1-3 animals/sex; Kupffer cell hypertrophy in 6/10 males and 10/10 females). In the animals fed 1000 ppm, effects observed were limited to a significant increase in forelimb and hind limb grip strength in males and females, increased number of band neutrophils in females, decreased haematocrit, haemoglobin, and mean erythrocyte volume values in males, and microscopic changes in the liver (bile duct hyperplasia in 1/10 males; necrosis in 1/10 males) and lymph nodes (macrophage hyperplasia in 1/10 males) of minimal severity. Apart from increased numbers of band

neutrophils in females, no effects were seen in the animals treated with 250 or 500 ppm of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol (NTP94).

Similar treatment of groups of 10 mice/sex resulted in doses of ca. 15, 30, 65, 145, or 345 mg/kg bw/day for males and of ca. 10, 35, 60, 165, and 340 mg/kg bw for females. In the 2500-ppm group, mean final body weights and mean body weight gains were significantly decreased in males (by 15 and 51%, respectively) and females (by 23 and 55%, respectively). During treatment, no toxic signs were noted. Changes in haematology and clinical chemistry values included statistically significant decreases in haematocrit, haemoglobin, erythrocyte count, and mean erythrocyte volume values in males and females. Relative weights of heart (females), kidney (females), liver (males, females), lung (males, females), spleen (males, females), and thymus (females) were increased. Upon microscopic examination, lesions of the liver (minimal bile duct hyperplasia in 10/10 males and 6/10 females; marked and moderately to marked Kupffer cell hyperplasia in 10/10 males and 10/10 females, respectively) and mesenteric lymph nodes (minimal and mild macrophage hyperplasia in 5/10 males and 1/10 females, respectively) were seen. Administration of 1000 ppm induced decreased mean final body weights (by 15%) and mean body weight gains (by 36%) in females, decreased haematocrit values and erythrocyte counts in males and females, and increased relative weights of spleen in males (by 17%; $p \leq 0.05$) and females (by 22%; $p \leq 0.01$)) and of heart, kidney, liver (by 10%; $p \leq 0.05$), and lungs in females. There were no remarkable microscopic findings. In the 500-ppm, there were only decreased mean final body weights and weight gains (by 11 and 28%, respectively) in females and increased relative spleen weights in males by 20%; $p \leq 0.05$) and females (by 12%; not significant) and increased relative heart, kidney, and lung weights in females. In the animals given 250 ppm, there were decreases in mean body weight gains (by 13%) and increased relative lung weights in females and not statistically significant increases in relative spleen weights in males (by 7%) and females (by 13%). At 100 ppm, changes in body weight gains (decrease by 20%) and relative lung weights (increase) were seen in females (NTP94).

In the 2-year toxicology and carcinogenicity study, groups of 115 male and 75 female rats were fed diets containing 0, 500, 1000, or 2500 ppm 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol, resulting in daily doses of ca. 20, 40, or 100 mg/kg bw for males and of ca. 20, 45, or 120 mg/kg bw for females. Haematology, clinical chemistry, and urinalysis evaluations were performed on 15 male and 15 female rats from each group at 3, 9, and 15 months, which were then discarded. An additional 10 male and 10 female rats from each group were also evaluated at 15 months for changes in haematology and clinical chemistry end points, after

which they were examined macroscopically and microscopically. Forty male rats per group underwent neurotoxicity evaluations including grip strength tests (in all 40 animals), electrophysiological tests (in 10), and neuropathological examinations (in 10). The remaining 20 animals were fed a control diet for an additional 13 weeks after which they were examined in a similar way (grip strength tests in 20; electrophysiology in 10; neuropathology in 10) to determine the reversibility of any effects. Administration of 2500 ppm did not affect survival rates. During treatment, there were no toxic signs noted. Body weights of male animals were generally ca. 3% lower than those of controls throughout most of the study; the final mean body weight was 5% lower. Female body weights started to decrease at week 12, being 14% and 6% lower than those of controls at week 65 and study termination, respectively. Results of the haematology evaluations were not uniformly consistent at 3, 9, and 15 months in one set of animals or between the two sets evaluated at 15 months. In males, slight, significant decreases in haematocrit, haemoglobin, and erythrocyte count values were seen in one set at 15 month, but not in the other set or in the sets evaluated at 3 and 9 months. In females, haemoglobin levels and mean erythrocyte haemoglobin counts were significantly decreased at 9 months and in both sets at 15 months while haematocrit levels were lower at 9 months only. Slightly but significantly increased platelet counts were observed in males and females at 3 and 9 months and in one set of males and the other set of females at 15 months. Results of clinical chemistry evaluations were generally similar at 3, 9, and 15 months, and included significant increases in serum alkaline phosphatase activities in males and in alanine transferase and sorbitol dehydrogenase activities in males and females at each time point. Urinalysis examinations showed a slight significant increase in N-acetyl-β-D-glucosamidase activity in females. Neurotoxicity testing at 3 and 6 months did not reveal effects on startle reflex, motor nerve excitability or conduction, neuromuscular transmission, or muscle contractility or microscopic lesions in the quadriceps muscle, the sciatic nerve or teased sciatic nerve preparations. Grip strength was tested in 8 trials instead of the standard 3. No differences were observed between exposed and control animals in the first trials at 3 months. Control animals performed worse in the later trials, apparently due to fatigue or habituation. Exposed animals demonstrated a similar impaired performance but less pronounced. Thus, grip strength in later trials (particularly that of the forelimbs) of the exposed group was significantly greater than that of controls. These effects were not seen at 6 months. At 15 months, there were significant increases in the relative liver weights of males (by 15%; $p \leq 0.01$) and females (by 25%; $p \leq 0.01$) and in the relative weights of kidneys (by 13%; $p \leq 0.01$) and spleen

(by 21%; p≤0.01) of females. Microscopic examination showed mainly effects on the liver (see Table 2). In the animals killed at 15 months, they included significant increases in the incidence of liver lesions, including Kupffer cell hypertrophy, cytoplasmic vacuolisation, basophilic foci, and mixed cell foci. The incidence of nephropathy was similar among all male and female groups as was the severity among male groups, but in females of the high-dose group, severity (2.2) was significantly greater when compared to controls. At the end of the study, similar effects were seen on the liver, apart from the basophilic foci, which showed similar incidences among all groups, and on the kidneys. In the animals given 1000 ppm, there were no effects on body weight. Results of haematology, clinical chemistry, and urinalysis evaluation only showed effects in males including slight, significant decreases in haematocrit, haemoglobin, and erythrocyte count values only in one 15-month set and significant increases in serum alkaline phosphatase only in both 15-month sets. The neurotoxicity tests showed a similar picture as at 2500 ppm, i.e., a better performance in the later trials of the grip strength at 3 months due to a lesser decrement when compared to controls. Apart from an increased relative liver weight in females (by 8%; p≤0.01), relative organ weights did not differ from those of controls. Upon microscopic evaluation, only effects on the liver were seen including increases in the incidences of cytoplasmic vacuolisation of minimal severity in males at 15 months and in females at terminal sacrifice and of mixed cell foci in males and females at terminal sacrifice (see Table 2). Apart from an increased incidence of hepatic cytoplasmic vacuolisation of minimal severity (see Table 2), no effects were observed in the 500-ppm group. Since the severity of cytoplasmic vacuolisation was similar in males of the 500- and 1000-ppm groups at 15 months and the incidences and severity of this hepatocytic findings did not differ significantly among the control, low- and mid-dose males at 2 years, the high incidence found in low-dose males at 15 months is regarded casual finding unrelated to treatment to 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol. With respect to neoplastic lesions, there were no statistically significant, treatment-related increases in the incidences of any tumour in any of the treated groups. For mammary gland tumours, there were significant negative trends in the incidences of fibroadenomas, decreases being significant in the mid- and high-dose group (controls: 29/50; 500 ppm: 24/50; 1000 ppm: 11/50; 2500 ppm: 16/50), and of fibroadenomas, adenomas, or carcinomas combined (32/50, 24/50, 11/50, 16/50, respectively) (NTP94).

Table 2 Incidences of non-neoplastic liver lesions in rats orally treated with 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol for 2 years (NTP94).

	males				females			
	0 ppm	500 ppm	1000 ppm	2500 ppm	0 ppm	500 ppm	1000 ppm	2500 ppm
15-month evaluation								
number of animals examined	10	10	7	10	10	10	10	10
Kupffer cell hyperplasia	0	0	0	10** (1.2)[a]	1 (1.0)	0	5 (1.0)	10** (2.7)
hepatocytic cytoplasmic vacuolisation	1 (1.0)	10** (1.1)	7** (1.0)	10** (1.7)	0	1 (1.0)	1 (1.0)	8** (1.0)
basophilic foci	5	2	7	10*	10	10	10	10
mixed cell foci	1	1	1	5	0	1	0	10**
2- year evaluation								
number of animals examined	50	50	50	49	50	50	50	50
Kupffer cell hyperplasia	2 (1.5)	3 (1.0)	2 (1.0)	31 (2.1)	11 (1.2)	10 (1.5)	9 (1.0)	42** (2.7)
hepatocytic cytoplasmic vacuolisation	13 (1.2)	11 (1.5)	19 (1.4)	18 (2.0)	12 (1.3)	10 (1.4)	20* (1.3)	34** (2.7)
fatty change					9 (1.4)	8 (1.5)	15 (1.3)	19* (1.5)
basophilic foci	18	22	23	22*	37	34	38	36
mixed cell foci	6	14	18*	15*	5	4	14*	34**

*p≤0.05, by the Fisher exact test (15-month evaluation) or the logistic regression test (terminal sacrifice). ** p≤0.01.

[a]   Average severity of lesions in affected animals; 1=minimal, 2=mild, 3=moderate, 4=marked.

Based on the slight liver effects seen in the 1000-ppm group (equivalent to 40-45 mg/kg bw/day), the committee concludes that the NOAEL in this 2-year rat feed study is 500 ppm or 20 mg/kg bw/day.

In the 2-year mouse study, groups of 80 males and 80 females were fed 0, 250, 500, or 1000 ppm, resulting in daily doses of ca. 30, 60, or 145 mg/kg bw for males and ca. 45, 110, or 255 mg/kg bw for females. Haematology and clinical chemistry evaluations were performed on 10 animals/sex/group at 3, 9, and 15 months while the animals killed at 15 months were examined macroscopically and microscopically. Treatment did not affect survival rates and no treatment-related clinical findings were seen in any of the groups. In the high-dose group, male body weights were ca. 10% lower than those of controls from week 45 through the end of the study. Female body weights were decreased by 11% at week 45 and 18% by the end of the study. In male mice, there were significant decreases in haematocrit, haemoglobin, erythrocyte count, and leukocyte count values at 15 months and increases in serum alkaline phosphatase activities at 3 and 9 months (also at 15 months, but not statistically significantly) and in serum total bilirubin levels at 9 and 15 months. In females, there was only an increase in serum alkaline phosphatase activity at 9 months. Relative organ weight changes included increases in weights of the kidneys (by 16%; p≤0.01)

and spleen (by 20 and 30%, respectively; $p \leq 0.05$ and ≤ 0.01, respectively) in males and females and of the liver (by 17%; $p \leq 0.01$) in females. At 500 ppm, the body weights of males were slightly lower and those of females ca. 9% lower when compared to controls. Apart from an increase in total bilirubin levels in serum of males at 9 and 15 months, no changes in haematology and clinical chemistry values were observed. Relative weights of kidneys, liver, and spleen did not differ statistically significantly from those of controls. In the 250-ppm groups, there were only slightly lower body weights in females (by ca. 9%; not significant) and increased serum total bilirubin levels in males at 9 and 15 months. Upon microscopic examination, only a few liver lesions were seen (cytoplasmic vacuolisation, fatty change, clear cell foci) and their incidences decreased with increasing dose levels. As to neoplastic lesions, there were no statistically significant, treatment-related increases in incidences of any tumour in any of the groups (NTP94). Based on the slight effects on body and relative organ weights and on haematology parameters at doses of 1000 ppm (equivalent to 145 and 255 mg/kg bw for males and females, respectively), the committee concludes that in the 2-year mice study, the NOAEL is 500 ppm, i.e., 60 and 110 mg/kg bw/day for males and females, respectively.

Mutagenicity and genotoxicity

6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol was negative when tested with and without metabolic activating systems in S. typhimurium strains TA97, TA98, TA100, TA102, TA1535, and TA1537 and in E. coli strain WP2/pKM102 (Hac87, Zei87). When tested with and without metabolic activation in Chinese hamster ovary cells, the compound induced sister chromatid exchanges (SCEs), at doses inducing cell cycle delay, but no chromosomal aberrations (NTP94).

Reproduction toxicity

In a screening study to evaluate the effects of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol on reproduction in female Swiss mice, oral administration of doses of 485 mg/kg bw/day to 50 pregnant mice on gestational days 6-15 induced maternal toxicity and a decreased pup survival rate, but did not affect the number of viable litters, litter size, pup birth weight, or pup weight gain (NTP94).

Immunotoxicity

The immunotoxic effects of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol were
evaluated in female B6C3F$_1$ mice (n=52-56/group) given oral (gavage) doses
(vehicle: corn oil) of 0, 10, 100, and 200 mg/kg bw for 14 days. General
toxicological (see Section 'Repeated-dose toxicity') and immune function end
points were investigated. Regarding immune function parameters (investigated
in 5-8 treated animals/group 24 hours after the last administration), the number
of spleen cells was significantly increased in the animals of the high-dose group,
in agreement with the increased spleen weights mentioned above; the number of
T cells was decreased at the mid ($p<0.01$) and high dose ($p<0.01$) while there
was no effect on the number of B cells at any of the doses. There was a dose-
related decrease in IgM and IgG antibody-forming cell (AFC) response to SRBC
(sheep red blood cells) reaching statistical significance at the high dose ($p<0.05$;
expressed as AFC/10^6 spleen cells); the delayed hypersensitivity response to
challenge with keyhole limpet haemocyanin was not affected. Treatment did not
induce proliferative responses to T-cell (concanavalin A and
phytohaemagglutinin) and B-cell mitogens (lipopolysaccharide). The mixed
lymphocyte response was decreased, reaching statistically significance ($p<0.05$)
at the low and high dose. The natural killer (NK) cell activity was increased at
the mid ($p<0.01$) and high dose ($p<0.05$), with the greatest increase at the mid
dose. Increases in serum complement (CH50) were found at the low ($p<0.01$)
and high dose ($p<0.05$); Holsapple et al. could not explain the lack of effect at the
mid dose. Effects on macrophage function were complex. There were no effects
on the phagocytic capabilities of the peritoneal exudates cells using either
fluorescent covaspheres (non-specific phagocytosis) or radiolabelled chicken red
blood cells (immune-Fc receptor-mediated phagocytosis). In the latter
experiment, a dose-related increase in the number of chicken red blood cells that
adhered to the peritoneal exudates cells was found, reaching statistically
significance ($p<0.01$) at the high dose. This suggested a compound-induced
increase in the number of Fc receptors on each peritoneal exudates cell.
Enhanced phagocytosis was also indicated by increased clearance of
radiolabelled chicken red blood cells from the circulation, associated with a
dose-dependent increase of the uptake of radioactivity in the liver, together with
a decreased uptake in spleen, lungs, and kidneys. Examined in 6 tests, host
resistance was not affected in Herpes simplex virus type 2, *L. monocytogenes*
and *P. berghei* while there were increases in resistance to *S. pneumoniae* and in
the B16F10 melanoma tumour model and decreases in the PYB6 tumour model.
These changes were dose dependent, reaching statistical significance at the mid

(B16F10 melanoma tumour model) and high dose (*S. pneumoniae*; B16F10 melanoma and PYB6 tumour models). From these data and the data presented by Munson et al. (see Section 'Repeated-dose toxicity'), Holsapple et al. concluded that 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol is capable of altering immunocompetence with subsequent changes in host resistance. The profile of the changes induced by 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol in immunocompetence is complex and required interpretation of a broad-based panel of assays measuring both acquired and innate immune capabilities as well as several toxicological end points such as haematology and clinical chemistry values and histology. The results of these investigations suggest that a component of the effects on immune function may be mediated by an effect of the test compound on the bone marrow (Hol88).

Table 3 Summary of effects on some immune function and liver parameters in female B6C3F$_1$ mice, orally (gavage) treated with 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol for 14 days (Hol88, Mun88).

parameter		number of animals	0 mg/kg bw	10 mg/kg bw	100 mg/kg bw	200 mg/kg bw
spleen weight:	relative (%)	8	0.38	0.43* (+13%)	0.52* (+37%)	0.50** (+32%)
	absolute (mg)		73	82*	105*	107**
liver weight:	relative (%)	8	5.1	5.4 (+6%)	5.6 (+10%)	7.0** (+37%)
	absolute (mg)		969	1033	1124**	1504**
	absolute (mg)[a]	6	892	1022**	1098**	1434**
mixed lymphocyte response responders + stimulators (number of spleen cells)[b]		7	25,942	15,701*	17,899	17,143*
serum complement (CH50 value)[c]		8	54	73**	58	83*

* p<0.05; ** p<0.01.

[a] For this different subset of animals, the relative liver weights were not given.

[b] Twenty-four hours after the last chemical exposure, animals were sacrificed and individual spleen cell suspensions were prepared. The proliferative response to mitomycine C-treated spleen cells from DBA/2 mice was measured. Responder cells from each treated animal were cultured alone or with the aforementioned stimulator cells (B6C3F$_1$ lymphocytes with and without DBA/2 lymphocytes).

[c] Twenty-four hours after the last chemical exposure, blood samples were taken. Serum complement levels were determined using a microtiter haemolytic assay. The CH50 is an arbitrary unit defined as the quantity of complement necessary for 50% lysis of erythrocytes under rigidly standardised conditions for sensitisation with antibody (Sti94).

From the data of Munson et al. (Mun88) and Holsapple et al. (Hol88) (see Table 3), the committee concludes that the lowest dose used in this study, 10 mg/kg bw, is a LOAEL for immunotoxic effects. The effects observed were: increased relative spleen and liver weights, decreased mixed lymphocyte response, and increased serum complement.

7   Existing guidelines

The current administrative occupational exposure limit (MAC) for 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol in the Netherlands is 10 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol in some other European countries and in the USA are summarised in the annex.

8   Assessment of health hazard

The committee did not find data on the biotransformation and kinetics of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol following exposure by inhalation. Following application of radiolabelled compound to the skin of mice and rats, 75 and 98-100%, respectively, of the radioactivity administered was recovered from the treated sites. After oral administration, absorption was stated to be incomplete (no quantitative data). After oral and intravenous administration, 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol was rapidly distributed throughout the body, primarily to the liver, and initially rapidly cleared from the tissues. From adipose tissue, liver, and skin, radioactivity was additionally cleared by a second slow phase. These fractions mainly consisted of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol suggesting that accumulation of parent compound in the liver and lipid-rich tissues might occur following repeated exposure. 6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol was primarily excreted into the faeces, mainly via the bile in the form of conjugated metabolites, and hardly (<2%) into the urine.

Human data are limited to two cases of contact dermatitis after wearing latex gloves. However, no positive allergic reactions were observed upon patch testing of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol (2% in petrolatum) in a group of 65 persons.

The committee did not find data from eye and skin irritation studies on 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol.

The committee did not find data from inhalation studies. Lethal toxicity data included oral LD$_{50}$ values of 2345 and 6900 mg/kg bw in rats and of 3200 mg/kg bw in rabbits, a dermal LD$_{50}$ of >1260 mg/kg bw in rabbits, and an intraperitoneal LD$_{50}$ of 50 mg/kg bw in mice.

Repeated dose studies included a 14-day gavage study in mice (as part of an immunotoxicity study) and 15-day, 13-week, and 2-year feed studies in rat and mice. In these studies, effects on the liver, kidney, spleen, and serum chemistry and haematology end points were observed. In the 2-year rat study, doses of 20,

40-45, and 120-125 mg/kg bw did not affect survival rates or induce overt signs of toxicity. At the high dose, body weights were slightly decreased. The liver appeared to be the target organ showing decreases in relative weight and significant increases in the incidences and (occasionally) severity of histological lesions such as Kupffer cell hypertrophy, cytoplasmic vacuolisation, fatty change basophilic foci, and mixed cell foci. Serum activities of alanine aminotransferase, alkaline phosphatase, and sorbitol hydrogenase were increased as well. Results of haematology evaluations at 3 and 9 months in one group of animals and at 15 months in two groups showed variable results. No effects were seen on the kidneys of male rats, but in high-dose females, relative weights and the severity of nephropathy were significantly increased when compared to controls. Treatment did not induce statistically significant increases in the incidences of any tumour in any of the treated groups. On the contrary, for mammary gland tumours, there were significant negative trends in the incidences of fibroadenomas, decreases being significant in the mid- and high-dose group, and of fibroadenomas, adenomas, or carcinomas combined. Based on the slight, but significant increase in the relative liver weights and in incidences of histological lesions in females at 45 mg/kg bw, the committee concludes that the NOAEL in this 2-year rat feed study is 20 mg/kg bw/day. In the 2-year mouse study, doses of 30, 60, and 145 or 45, 110, and 255 mg/kg bw for males and females, respectively, did not affect survival rate or induce overt signs of toxicity. In all dose groups, body weights were lower than those in controls (by ca. 9%), but reached only statistically significance in high-dose females (decrease: 18%). In high-dose animals, haematology parameters were affected and relative weights of spleen, kidneys, and liver were increased. There were no treatment-related histopathological adverse effects. It is remarkable that the incidences of liver lesions in male mice tended to decrease with increasing doses. Treatment did not induce statistically significant increases in the incidences of any tumour in any of the treated groups. Based on the slight effects on body and relative organ weights and on haematology parameters at doses of 145 and 255 mg/kg bw, the committee concludes that in the 2-year mouse study, the NOAEL is 60 and 110 mg/kg bw/day for males and females, respectively.

6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol was not neurotoxic when tested (forelimb and hind limb grip strength, startle response, tail flick, foot splay) in male and female rats during the final 8 days of a 13-week exposure to dietary doses of 165-170 mg/kg bw/day or in male rats (grip strength, startle reflex, electrophysiology tests, neuropathology) immediately after exposure to dietary doses of 100 mg/kg bw/day for 3 months or after a subsequent exposure-free period of 3 months.

6,6'-Di-*tert*-butyl-4,4'-thiodi-*m*-cresol did not induce mutations in *in vitro* bacterial (*S. typhimurium, E. coli*) test systems. In Chinese hamster ovary cells, it did not cause chromosomal aberrations but at doses inducing cell cycle delay, there was an increase in the frequency of SCEs.

Oral administration of doses of 485 mg/kg bw/day to mice on gestational day 6-15 resulted in maternal toxicity and decreased pup survival rates, but the number of viable litters, litter size, pup birth weight, or pup weight gain were not affected.

Oral (gavage) administration of doses of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol of 10, 100, and 200 mg/kg bw, for 15 days, to female mice generally showed complex responses on immune function parameters concerning humoral and cell-mediated immunity, macrophage function, and host resistance. The committee could not establish a NOAEL since effects including increased relative spleen and liver weights, decreased mixed lymphocyte response, and increased serum complement were observed at 10 mg/kg bw, the lowest dose tested.

The results of this 14-day gavage study in female mice (Hol88, Mun88) suggest that doses as low as 10 mg/kg bw/day might affect the immune system. However, from the lack of effects on survival rate, incidences of neoplastic or non-neoplastic lesions in females of the same strain of mice exposed for 2 years at slightly higher doses via the diet, the committee concludes that the modulation of the immune system, found after subacute exposure, does not impair the overall resistance of the animals against microbial infections or immune-mediated diseases, nor does it increase the tumour incidence. Therefore, the committee does not consider the immune system the critical target of 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol.

From the 2-year NTP studies (NTP94), the committee concludes that rats are more sensitive to exposure to long-term to 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol and takes the NOAEL of 20 mg/kg bw/day as a starting point for deriving a health-based recommended exposure limit (HBROEL). Since workers are exposed for 5 days a week, this NOAEL from a continuous study (i.e., 7 days/ week) is adjusted by multiplying it with a factor of 7/5 resulting in a calculated no-adverse-effect level (NAEL) of 28 mg/kg bw. For the extrapolation to an HBROEL, a factor of 4 for allometric scaling from rats to humans, based on caloric demand, and an overall factor of 9, covering inter- and intraspecies variation, are applied, resulting in a NAEL for humans of 0.78 mg/kg bw. Assuming a 70-kg worker inhales 10 m^3 during an 8-hour working day and a retention of 100%, and applying the preferred-value approach, a health-based

occupational exposure limit of 5 mg/m^3 is recommended for 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol.

The committee recommends a health-based occupational exposure limit for 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol of 5 mg/m^3, as inhalable dust, as an 8-hour time-weighted average.

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Annex

Occupational exposure limits for 6,6'-di-*tert*-butyl-4,4'-thiodi-*m*-cresol in various countries.

country - organisation	occupational exposure limit		time-weighted average	type of exposure limit	note[a]	reference[b]
	ppm	mg/m^3				
the Netherlands - Ministry of Social Affairs and Employment	-	10	8 h	administrative		SZW05
Germany - AGS	-	-				TRG04
- DFG MAK-Kommission	-	-				DFG05
Great Britain - HSE	-	10	8 h	OES		HSE03
	-	20	15 min			
Sweden	-	-				Swe00
Denmark	-	10	8 h			Arb02
USA - ACGIH	-	10	8 h	TLV	A4[e]	ACG05
- OSHA	-	15[c]	8 h	PEL		ACG04
	-	5[d]	8 h	PEL		
- NIOSH	-	10[c]	10 h	REL		ACG04
	-	5[d]	10 h	REL		
European Union - SCOEL	-	-				EC05

[a]   S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

[b]   Reference to the most recent official publication of occupational exposure limits.

[c]   Total dust.

[d]   Respirable fraction.

[e]   Classified in carcinogenicity category A4, i.e., not classifiable as a human carcinogen: agents which cause concern that they could be carcinogenic for humans but which cannot be assessed conclusively because of a lack of data. *In vitro* or animal studies do not provide indications of carcinogenicity which are sufficient to classify the agent into one of the other categories.