Tricresylphosphate

Evaluation of the effects on reproduction, recommendation for classification

To: the Minister of Social Affairs and Employment
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Health Council of the Netherlands

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samenvatting

Werknemers kunnen tijdens het werk worden blootgesteld aan stoffen die mogelijk schadelijk zijn voor hun gezondheid. Op verzoek van de minister van Sociale Zaken en Werkgelegenheid (SZW) heeft de Gezondheidsraad beoordeeld of tricresylfosfaat (tricresylphosphate (TCP)) schadelijke eigenschappen heeft die invloed kunnen hebben op de voortplanting.

Dit advies is tot stand gekomen in de Subcommissie Classificatie reproductie toxische stoffen, van de Commissie Gezondheid en beroepsmatige blootstelling (GBBS). Op www.gezondheidsraad.nl staat informatie over de taken van deze vaste commissie van de Gezondheidsraad. De samenstelling van de subcommissie is te vinden achterin dit advies.

Gebruik van tricresylfosfaat

Tricresylfosfaat wordt gebruikt als vlamvertrager in polystyreen en andere thermoplasten, als PVC-weekmaker, smeermiddel en als hydraulische vloeistof. Het wordt gebruikt in beroepsmatige omgevingen zoals in drukkerijen, in formulering van mengsels en in wetenschappelijk onderzoek. Tricresylfosfaat wordt ook gebruikt als additief in motorolie van vliegtuigen.

Classificeren naar bewijskracht

Bij de beoordeling van effecten op de voortplanting kijkt de commissie zowel naar effecten op de vruchtbaarheid van mannen en vrouwen als naar effecten op de ontwikkeling van het nageslacht. Daarnaast worden effecten op de lactatie (productie en afgifte van moedermelk) beoordeeld en effecten via de moedermelk op de zuigeling. Als er aanwijzingen bestaan dat de stof schadelijke effecten heeft, stelt de commissie voor om de stof te classificeren in gevarencategorieën die aangeven hoe groot de bewijskracht is voor de schadelijke effecten, zie kader. Bij categorie 1 is de bewijskracht het grootst en grotendeels gebaseerd op studies bij mensen (1A) of dieren (1B). Bij categorie 2 is de bewijskracht beperkt en is er sprake van een ‘verdenking’. De commissie kan ook adviseren om een stof niet te classificeren omdat er onvoldoende gegevens beschikbaar zijn of omdat de stof waarschijnlijk niet schadelijk is voor de voortplanting. Een classificatievoorstel zegt iets over de bewijskracht voor de schadelijke eigenschappen van een stof, maar niet over de mate waarin mensen op de werkplek een gezondheidsrisico lopen. Dat hangt namelijk af van de mate waarin mensen op hun werk worden blootgesteld aan de stof. Daar heeft de commissie geen zicht op.

Geraadpleegde onderzoeken

Er zijn geen gegevens beschikbaar uit onderzoeken onder mensen.

Met betrekking tot de effecten van blootstelling aan tricresylfosfaat op de vruchtbaarheid is een beperkte hoeveelheid gegevens beschikbaar uit dierstudies. Die gegevens wijzen op een verminderde vruchtbaarheid bij ratten na blootstelling aan tricresylfosfaat. Over de effecten op de ontwikkeling is slechts één dierstudie beschikbaar. De gegevens uit die studie geven aanleiding tot bezorgdheid. Zo werd er een verband gevonden tussen blootstelling aan tricresylfosfaat en een lager lichaamsgewicht van de foetussen. Of er sprake is van een effect op de ontwikkeling is onduidelijk, omdat er ook bij de moederdieren sprake was van een verminderde gewichtstoename.

Er waren geen gegevens beschikbaar om de effecten van blootstelling aan tricresylfosfaat op of via lactatie te beoordelen.

Advies aan de minister

Op basis van de beschikbare wetenschappelijke gegevens adviseert de commissie om tricresylfosfaat:

- te classificeren als een stof die ervan verdacht wordt schadelijk te zijn voor de vruchtbaarheid (categorie 2) en te kenmerken met H361f (verdacht van het schaden van vruchtbaarheid);
- niet te classificeren voor effecten op de ontwikkeling omdat er onvoldoende geschikte onderzoeksgegevens zijn;
- niet te classificeren voor de effecten op of via lactatie omdat er geen onderzoeksgegevens zijn.

Betekenis classificatievoorstellen

In classificatievoorstellen gebruikt de Gezondheidsraad een indeling in gevarencategorieën. De categorieën zijn afgeleid van EU-verordening (EG) 1272/2008 en geven aan hoe sterk de bewijskracht is voor schadelijke effecten.

EU-gevarencategorieën voor reproductie toxische stoffen

- Categorie 1 Kan de vruchtbaarheid of het ongeboren kind schaden (EU-gevarenaanduiding H360)
  - *Categorie 1A* Stoffen waarvan *bekend* is dat zij toxisch zijn voor de menselijke voortplanting (hoofdzakelijk gebaseerd op gegevens bij mensen).
  - *Categorie 1B* Stoffen waarvan *verondersteld wordt* dat zij toxisch zijn voor de menselijke voortplanting (hoofdzakelijk gebaseerd op dierstudies).
- Categorie 2 Kan mogelijk de vruchtbaarheid of het ongeboren kind schaden (EU-gevarenaanduiding H361). Stoffen die ervan *verdacht* worden dat zij toxisch zijn voor de menselijke voortplanting

EU-gevarencategorie voor effecten op of via lactatie

- Kan schadelijk zijn via de borstvoeding (EU-gevarenaanduiding H362). Stoffen waarvan is aangetoond dat zij de lactatie beïnvloeden of die in zodanige hoeveelheden in moedermelk aanwezig kunnen zijn dat er reden is tot bezorgdheid voor de gezondheid van het kind dat borstvoeding krijgt.

Betekenis voor de werkvloer

Werkgevers zijn op grond van de Arbowet wettelijk verplicht om gezondheids- en veiligheidsrisico’s van het werken met stoffen zoveel mogelijk te voorkomen of te beperken. Op basis van de classificatievoorstellen van de Gezondheidsraad kan de minister van SZW besluiten stoffen op te nemen in de officiële lijst van kanker-verwekkende, mutagene en voor de voortplanting giftige stoffen.

Op die lijst staan kankerverwekkende en mutagene stoffen in categorie 1A en 1B en voor de voortplanting giftige stoffen in categorie 1A, 1B en 2. Afhankelijk van de classificatie vraagt de wetgever de werkgever aanvullende maatregelen te nemen om de werknemer te beschermen.

executive summary

At the request of the Minister of Social Affairs and Employment, the Health Council of the Netherlands evaluated the effects of tricresylphosphate on reproduction. This advisory report was drafted by the Subcommittee on the Classification of Substances Toxic to Reproduction of the Dutch Expert Committee on Occupational Safety (DECOS) of the Health Council, hereafter called the Committee. The Health Council has a permanent task in assessing the hazard of substances to which man can be occupationally exposed. More information about this task can be found at www.gezondheidsraad.nl.

Use of tricresylphosphate

Tricresylphosphate (TCP) is used as a flame retardant in polystyrene and other thermoplastics, as a PVC plasticiser, lubricant and as hydraulic fluid. It is used in occupational settings such as in the media printing industry, formulation of mixtures and scientific research. TCP is also used as additive in turbine engine oil.

Classification based on evidence

To assess effects on reproduction, the Committee evaluates the effects on male and female fertility and on the development of the offspring. Moreover, the Committee considers effects of a substance on lactation and on the offspring via lactation. If the data indicate hazardous properties, the Committee recommends classification in a hazard category. The classification is performed according to EU-regulation (EC) 1272/2008.

Reviewed literature

No human data were available. There were limited data from animal studies available regarding effects of exposure to TCP on fertility and developmental effects. The fertility study showed reduced fertility in rats after exposure to TCP. The available data on functional developmental effects indicated concerns, but are not sufficient for classification.
No data were available to assess the effects of exposure to TCP on or via lactation.

Recommendations to the Minister

Based on the available scientific data, the Committee recommends:

- to classify TCP as suspected to be a reproductive toxicant to humans, which corresponds with category 2 for reproduction, and to label TCP with H361f (suspected of damaging fertility);

- not to classify TCP for developmental toxicity due to a lack of appropriate data;
- not to classify TCP for effects during lactation due to a lack of data.

01 scope

1.1 Background

As a result of the Dutch regulation on registration of compounds toxic to reproduction that came into force on April 1st 1995, the Minister of Social Affairs and Employment requested the Health Council of the Netherlands to classify compounds toxic to reproduction. This classification is performed by the Health Council's Subcommittee on the Classification of Substances Toxic to Reproduction of the Dutch Expert Committee on Occupational Safety (DECOS). The classification is performed according to European Union Regulation (EC) 1272/2008 on classification, labelling and packaging (CLP) of substances and mixtures. The CLP regulation is based on the Globally Harmonised System of Classification and Labelling of Chemicals (GHS). The Subcommittee's advice on the classification will be applied by the Ministry of Social Affairs and Employment to extend the existing list of compounds classified as reproductive toxicant (category 1A and 1B and 2) or compounds with effects on or via lactation.

1.2 Committee and procedure

This document comprises the recommendations for classification of tricresylphosphate (TCP) by the Health Council's Subcommittee on the Classification of Substances Toxic to Reproduction, hereafter called the Committee. The members of the Committee are listed on the last page of this report. The classification is based on the evaluation of published human and animal studies concerning adverse effects with respect to fertility and offspring development as well as adverse effects on or via lactation.

Classification for reproduction (fertility (F) and development (D)):

- Category 1 Known or presumed human reproductive toxicant (H360(F/D)).
- Category 1A Known human reproductive toxicant.
- Category 1B Presumed human reproductive toxicant.
- Category 2 Suspected human reproductive toxicant (H361(f/d)).
- No classification for effects on fertility or development.

Classification for lactation:

- Effects on or via lactation (H362).
- No labelling for lactation.

Hazard statement codes:

H360F	May damage fertility.
H360D	May damage the unborn child.
H361f	Suspected of damaging fertility.
H361d	Suspected of damaging the unborn child.
H360FD	May damage fertility. May damage the unborn child.
H361fd	Suspected of damaging fertility. Suspected of damaging the unborn child.

H360Fd May damage fertility. Suspected of damaging the unborn child.
H360Df May damage the unborn child. Suspected of damaging fertility.
H362 May cause harm to breast-fed children.

The classification and labelling of substances is performed according to the guidelines of the European Union (Regulation (EC) 1272/2008).
The classification of compounds is the result of an integrated assessment of the nature of all parental and developmental effects observed, their specificity and adversity, and the dosages at which the various effects occur. The guideline necessarily leaves room for interpretation, dependent on the specific data set under consideration. In the process of using the regulation, the Committee has agreed upon a number of additional considerations.

Additional considerations to Regulation (EC) 1272/2008

If there is sufficient evidence to establish a causal relationship between human exposure to the substance and impaired fertility or subsequent developmental toxic effects in the offspring, the compound will be classified in category 1A, irrespective of the general toxic effects (see Regulation (EC) 1272/2008, 3.7.2.2.1.).

Adverse effects in a reproductive study, reported without information on the paternal or maternal toxicity, may lead to a classification other than category 1B, when the effects occur at dose levels which cause severe toxicity in general toxicity studies.

Clear adverse reproductive effects will not be disregarded on the basis of reversibility per se.

The Committee does not only use guideline studies (studies performed according to OECD[a] standard protocols) for the classification of compounds, but non-guideline studies are taken into consideration as well.

Regarding fertility, the Committee considers data on parameters related to fertility, such as seminal fluid volume and spermatozoa concentration, that are related to male fertility. The Committee excludes publications containing only data on sex hormone levels from the assessment, because the relationship between these hormone levels and functional fertility (ability to conceive children) is too uncertain.

[a] Organisation for Economic Cooperation and Development

In 2023, the President of the Health Council released a draft of the report for public review. The Committee has taken the comments received into account in deciding on the final version of the report. These comments, and the replies by the Committee, can be found on the website of the Health Council.

1.3 Labelling for lactation

The recommendation for classifying substances for effects on or via lactation is also based on Regulation (EC) 1272/2008. The criteria define that substances which are absorbed by women and have been shown to interfere with lactation or which may be present (including metabolites) in breast milk in amounts sufficient to cause concern for the health of a breastfed child, shall be classified and labelled. Unlike the classification of substances for fertility and developmental effects, which is based on hazard identification only (largely independent of dosage), the labelling for effects on or via lactation is based on a risk characterization and therefore, it also includes consideration of the level of exposure of the breastfed child.

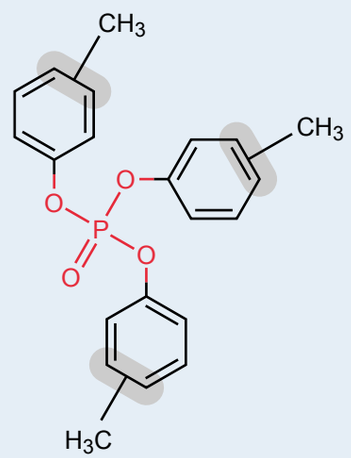
Consequently, a substance should be labelled for effects on or via lactation when it is likely that the substance would be present in breast milk at potentially toxic levels. The Committee considers a concentration of a compound as potentially toxic to the breastfed child when this concentration leads to exceeding the exposure limit for children, or if that level is unknown, the exposure limit for the general population, e.g. the acceptable daily intake (ADI).

1.4 Data

A literature search for publications on reproductive toxicity of TCP was performed using various databases up to September 2022, with an additional search using “tricresyl phosphate reproductive”. Additionally, the search strategy included publications on (toxico)kinetics and monitoring. Details on the literature search strategy can be found in annex B.

02 identity of the substance

2.1 Name and other identifiers of the substance

Name(s) in the IUPAC nomenclature or other international chemical name(s)	**tris(4-methylphenyl) phosphate**
Other names (usual name, trade name, abbreviation)	Tricresylphosphate, tris(2-methylphenyl) phosphate, tritolyl phosphate, Tris(methylphenyl) phosphate, TCP
ISO common name (if available and appropriate)	
EC/EINECS number (if available and appropriate)	809-930-9
EC name (if available and appropriate)	
CAS number	1330-78-5
Other identity code (if available)	1259372-53-6, 2107376-26-9, 25013-17-6, 34902-62-0, 56499-45-7, 56573-10-5, 69234-04-4, 73299-28-2
Molecular formula	C21H21O4P
Structural formula	
SMILES notation (if available)	
Molecular weight or molecular weight range	368.4 g/mol
Degree of purity (%)	>= 87 - <= 100 % (w/w)

2.2 Composition of the substance

TCP consists of multiple isomers and is registered as a multi-constituent substance in the REACH-dossier. The composition consists of tri-m-cresylphosphate (CAS 653-04-2), 4-methylphenyl di-3-methylphenyl phosphate, and 3-methylphenyl di-4-methylphenyl phosphate. Formation of the neurotoxic o-isomer (tri-o-tolyl phosphate (TOCP)) is prevented as much as possible during manufacturing of the commercial products and this isomer occurs only as an impurity.[1, 2] The presence of one or more o-tolyl groups among the three phenolic moieties of TCP is considered necessary to induce these neurotoxic effects.[a] Therefore, the presence of TOCP can complicate the evaluation of TCP. According to the guidelines for classification (see section 1.2), a multi-constituent substance is classified as category Repro 1B if a constituent is already classified as category Repro 1B and is present at more than 0.3% in the substance. If a constituent is classified as category Repro 2, the limit is 3%.
The Committee therefore considers only studies where TCP contains <0.3% TOCP.

The Committee notes that a continuous breeding study is referenced in the REACH dossier of TCP in support of a self-classification for effects on fertility. This continuous breeding study was first described in a National Toxicology Program (NTP) report in 1985 and the data were later

[a] https://www.inchem.org/documents/ehc/ehc/ehc110.htm#SectionNumber:10.1

published by Chapin et al. (1988).[3, 4] In this publication, the specified amount of pure TOCP is <0.1%. However, it is also stated that the amount of pure and/or mixed ortho- meta- and para-cresyl isomers composed 74.9% of the total, leading to uncertainty regarding the total amount of ortho-cresyl isomers. Therefore, this study is not further considered for evaluation.

2.3 Physico-chemical properties

State of substance at normal temperature and pressure	**Liquid**
Melting/freezing point	-20 °C
Boiling point	400 °C
Density	1.172 g/cm^3
Partition coefficient (Log Kow)	5.93
Water solubility	0.271 mg/L
Viscosity	80 mPa · s (dynamic)

2.4 International classifications

No European harmonized classifications exist for TCP (CAS 1330-78-5). Some notified self classification and labelling data were mentioned for reproduction (H361) based on testicular effects and sperm concentration and motility.

03 manufacture and uses

3.1 Manufacture

TCP is a multi-constituent substance that is formulated in a mixture of isomers. Commercial TCP is manufactured by reaction of phosphorous oxychloride with a mixture of alkyl phenols derived from petroleum or coal tar.[5] The major components that are formed within this reaction are based on m-cresol and p-cresol. The levels of o-alkyl phenols are minimized by the manufacturers to avoid production of o-isomers.

3.2 Identified uses

TCP is used as a flame retardant in polystyrene and other thermoplastics, as a PVC plasticiser, lubricant and as hydraulic fluid.[2] TCP is used in occupational settings such as in the media printing industry, formulation of mixtures and scientific research. TCP is also used as additive in turbine engine oil. TCP is manufactured in and/or imported to the EU at >/= 1000 to <10 000 tonnes per year.

04 toxicokinetics

The available information on toxicokinetics for TCP was limited to one study on the p-isomer. Kurebayashi et al studied tri-p-cresylphosphate (TPCP) in male Wistar rats by orally administrating 7.8 mg/kg or 89.6 mg/kg [^{14}C]TPCP in DMSO and evaluated the toxicokinetic properties of TPCP related to absorption, distribution, metabolism and elimination.[6] The authors did not define the exact location of the radiolabel in the TPCP molecule.

4.1 Absorption

Following oral administration TPCP was absorbed from the intestines. The authors conclude that the main faecal metabolite was unchanged TPCP, indicative of incomplete absorption.[4]

4.2 Distribution

After 24, 72 and 168 hours of oral administration (89.6 mg/kg) in rats, the radioactivity was relatively high in adipose tissue, liver and kidney. Also, the stomach and intestine showed radioactivity. Intermediate radioactivity was detected in blood, thymus, spleen, testes and lungs. The brain, muscle and heart contained the least amount of reactivity. Overall, after 72 hours the concentrations were reduced to one fourth of the concentrations at 24 hours. This was decreased to one-tenth at 168 hours.

4.3 Metabolism

TPCP was metabolized by oxidation and diarylation. Using radiolabelled TPCP, Kurebayashi et al. proposed a metabolic pathway starting with TPCP being absorbed by the gastrointestinal tract after which it gets oxidized to di-p-cresyl p-carboxyphenyl phosphate (1coTPCP) and p-cresyl di-p-carboxyphenyl phosphate (2coTPCP) in the liver. These triesters are excreted through the bile after which they get deesterified in the intestine. The intestinal microflora would degrade part of the p-hydroxybenzoic acid to CO_2.

4.4 Elimination

In rats, TPCP and its metabolites were excreted in the urine, bile, faeces and breath. The oral 7.8 mg/kg administered [methyl-^{14}C]TPCP was excreted in the urine (41%) and faeces (44%) within 7 days. For 3 days, the excretion through breath expressed in $^{14}CO_2$ was 18% of the radioactivity. In individual rats, the biliary excretion was 28% of the 7.8 mg/kg administered dose after 24 hours. At a dose of 89.6 mg/kg the radioactivity in urine was 12% and in faeces was 77% after 7 days. In air this was 6% after 3 days.

The major excreted urinary metabolites were p-hydroxybenzoic acid, di-p-cresyl phosphate, and p-cresyl p-carboxyphenyl phosphate. The metabolites excreted in the bile were di-p-cresyl phosphate, p-carboxyphenyl phosphate, and the oxidized triesters, 1coTPCP and

2coTPCP. The main excreted faecal substances were TPCP or similar to those of bile.

05 toxicity to reproduction

No human data were available related to TCP and reproductive or developmental effects.

5.1 Animal studies

The studies in which animals were exposed to TCP are summarized in annex A.

5.1.1 Fertility studies

Latendresse et al (1994) examined the effects on reproduction after an oral administration of BTP (butylated triphenyl phosphate; CAS 115-86-6) or TCP (CAS 1330-78-5, as a positive control) in F-344 rats (20 breeding pairs per group).[7] TCP was composed of mostly p- and m-isomers (62 wt%) of TCP and a mixture of substantial amounts of cresyl-xylyl (18 wt%) and cresyl-ethylphenyl (18 wt%) phosphates. No o-isomer (TOCP) was detected. A naive control group and vehicle (sesame oil) control group (40 breeding pairs) were also included. The dosing of test groups consisted of 600 mg, 1,000 g or 1,700 mg BTP/kg/day or only one dose group of 400 mg TCP/kg bw/day. In phase 1 of the study, a continuous breeding period allowed birth of multiple litters per breeding pair and a postbreeding interval. The continuous breeding period provided a constant breeding challenge with the possibility for all spermatogenesis phases to complete. Immediately after the postbreeding interval of phase 1, phase 2 was started which consisted of a cross-over mating period. Based on the fact that naive and vehicle control groups showed no differences in phase 1, indicative of no effects of gavaging or daily handling, the following schedule was selected for phase 2: Naive control males were mated with naive control females and vehicle controls were mated with TCP treated animals for 8 days followed by a 28-day period for the females to deliver their offspring.

Effects on reproduction of TCP were found during phase 1 in terms of a decreased fertility index (the percentage of cohabited pairs producing one or more (live or dead) litters) and fewer litters per breeding pair. Furthermore, the number of live pups per litter was decreased (6.67 ± 1.26 vs. 10.15 ± 0.04 in controls (mean ± standard error, $p \leq 0.05$)). The proportions of pups born alive was not affected indicating a reduced litter size, suggesting an effect on fertility rather than on development. Cross-over mating in phase 2 of TCP treated males with control females resulted in a mating index of 84.2% (controls 100%), but resulted in no offspring indicating complete infertility in males. This was not observed after cross-over mating of TCP treated females with control males for which the reproductive efficiency did not differ from controls. In TCP treated groups, testicular and epididymal weights were decreased and ovarian weights were increased as compared to controls. Additionally, an increase in adrenal gland and liver weight was detected in the TCP treated rats as compared to controls. An additional general toxic effect of TCP

was noted as a decrease in body weight was observed in males after 96 days (part of phase 1) and in females after 131 days (part of phase 2).

5.1.2 Repeated dose studies assessing effects on reproductive organs

Somkuti et al (1987) tested the effects of TOCP and TPCP in male rats and assessed the effects on their reproductive organs during subchronic administration of 63 days.[8] One dose of TPCP was tested of 100 mg/kg/day by gavage in male F-344 rats. No general toxic effects were observed. Testosterone values in testicular interstitial fluid were 25% lower than controls and a lower epididymal sperm density was observed as compared to controls. TPCP administration had no effect on testicular morphology or sperm morphology and motility.

Latendresse et al (1993) administered TCP and butylated triphenyl phosphate (BTP) to female F-344 rats and studied the effects on their reproductive organs in a study of 40 days.[9] TCP was composed of mostly p- and m-isomers and a mixture of cresyl-xylyl, cresyl-ethylphenyl, and ethylphenyl-xylyl phosphates. No o-isomer TCP was detected. Only one dose group was investigated of 400 mg TCP/kg/day by gavage, which affected the adrenal glands and resulted also in increased ovarian weights with hypertrophy and cytoplasmic vacuolization of interstitial cells.

Conclusion on fertility

Exposure to a single dose of 400 mg TCP/kg bw leads to a reduced fertility in rats (decreased fertility index and fewer litters per breeding pair).[7] Furthermore, treated males were incapable to produce offspring after confirmed mating with untreated females in a cross-over study. Furthermore, effects were observed also on reproductive organs in male and female exposed animals as compared to controls with respect to testicular, epididymal (both decreased) and ovarian (increased) weights.[9, 10]

The Committee concludes that classification for effects on fertility is warranted as in rats severe effects on fertility and reproductive organs have been observed in a reproductive toxicity study. These effects however, have only been observed in one non-guideline study in which only one dose was applied. The Committee therefore considers the available evidence insufficient for a classification in Category 1B and recommends classifying TCP in Category 2.

5.1.3 Developmental studies

In an EPA OPPTS 870.3700-guideline developmental toxicity study in rats, no effects on pup viability were observed.[11] In this study, a to the Committee unknown isomer composition of TCP was administered to female rats in dosages of 20, 100, 400, and 750 mg/kg/day from gestation day 0 to gestation day 19. Effects on body weights and body weight gains were observed at the two highest dose groups in a dose-responsive

manner. Over a period of day 18-20 of gestation, the 400 mg/kg bw/day dosed rats gained 22 grams and the rats dosed 750 mg/kg bw/day lost 0.3 grams, whereas the controls were gaining 35 grams. Over the entire 0-20 day gestational period, the 400 mg/kg bw/day dosed rats gained 126.5 grams (14% lower than controls (146.6 grams), $p<0.01$), and the 750 mg/kg bw/day dosed rats gained 94.9 grams (35% lower than controls, $p<0.01$). Food consumption was statistically lower in the 750 mg/kg/day group as compared to controls. The dose groups 400 and 750 mg/kg/day exhibited lower gravid uterine weights as compared to controls. Also, the adjusted GD20 body weights (body weight minus uterine weight) and adjusted body weight gains (GD0-20) were lower in the 750 mg/kg/day group as compared to controls. The authors considered this effect likely to be secondary to the reduced foetal body weights, which were below historical control data.

No effects were seen on the number of dead or live foetuses at scheduled necropsy. Developmental effects were observed in all dose groups by means of statistically significant reduced foetal body weights. Compared to controls that weighed 3.76 g, reductions were reported in a range of 4.4-6.3% for 20 and 100 mg/kg bw, and as reductions of 9% and 18%, in the 400 and 750 mg dose groups, respectively. The foetal body weight of controls was within historical control values, although in the lower limit range. In all dose groups foetal body weights were below the historical controls. In the highest dose group, also incomplete ossified bones were found including unossified sternebrae. Various incidental findings were observed at all dose levels which were not statistically significant from controls, specifically at the external level (gastroschisis, mouth, jaw eyes), visceral level (renal pelvic cavitation) and skeletal level (misshapen squamosal bone and small mandible, absent jugal bone and small squamosals, absent rib and defects of lumbar and thoracic vertebrae).

Conclusion on development

Dose-dependent reduced foetal body weights (below historical control data) have been observed in a guideline-compliant developmental study in rats. Incidental findings of malformation were found at all doses and in the highest dose group incomplete ossified bones were reported. At the two highest doses reduced maternal weight gain was observed. As such, it could not be excluded that the observed effects on foetal body weights were secondary to the observed maternal toxicity.

The Committee concludes that the available evidence from this developmental study raises concerns, but is not conclusive, for functional developmental effects after exposure to TCP. The Committee therefore concludes that a classification for developmental toxicity is not possible based on the available data.

5.1.4 Lactation studies

No studies were found regarding the effects of TCP on or via lactation in animals.

06 conclusions on classification and labelling

The Committee recommends classification according to Regulation (EC) 1272/2008 of the European Union. TCP is regarded as a mixture of isomers for which the composition can differ. The consulted studies that are described within this advisory report reflect the effects of TCP on fertility and development of offspring. From the described evidence for TCP, the Committee concludes the following:

Proposed classification for fertility

Category 2, H361f.

Proposed classification for developmental toxicity

Lack of appropriate data precludes the assessment of TCP for effects on development.

Proposed labelling for effects on or via lactation

Lack of data precludes the assessment of TCP for effects on or via lactation.

references

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annex A

supplementary tables

Table 1 Fertility studies

Reference	Species	Dose/route	Experimental period/design	General toxicity	Effects on reproduction
Latendresse et al. (1994)	Rats (F-344), 20 breeding pairs per group	0.4 g TCP/kg/day oral dose in sesame oil	Phase 1: 98-day period; 7 days before pairing, 63-day breeding period, and 28-day postbreeding interval. Phase 2: immediate follow-up of phase 1 with crossover mating for 8 days with 28-day cohabitation period for females to deliver. Assessment of body weights, fertility rate, number of litters/pups, proportion live/dead pups, body weights pups. Phase 2: also organ weights	• decrease in body weight: males 9.2% compared to controls on day 96 (=phase 1) and females 6.5% compared to controls on day 131 (=phase 2) Phase 2: • increase in adrenal gland weight (males: 160 mg +/- 10 in TCP group vs. 60 mg +/- 0 in controls; females: 140 mg +/- 10 in TCP group vs. 60 mg +/- 0 in controls) • increase in liver weight (males: 17.43 g +/- 0.25 in TCP group vs. 13.24 g +/- 0.25 in controls. females: 10.34 g +/- 0.16 in TCP group vs. 8.18 g +/- 0.15 in controls)	Phase 1: • decreased fertility index of approximately 45% in the TCP group vs. 100% in controls. • fewer litters per fertile pair. 0.5 litters in the TCP group vs. 2.7 in controls. • number of live pups per litter was decreased in TCP group compared to control group. All other parameters not affected (including portion of live / litter). Phase 2: • TCP male rats produced no litters • decreased testicular weight (2.16 g +/- 0.07 in TCP group vs 3.09 g +/- 0.02 in controls) and epididymal weights (710 mg +/- 20 in TCP group vs. 970 mg +/- 10 in controls) • increased ovarian weight (170 +/- 10 mg in TCP group vs. 130 mg +/- 0 in controls)

Table 2 Repeated dose toxicity studies assessing effects on reproductive organs

Literature	Species	Dose/route	Experimental period/design	General toxicity	Effects on reproductive organs
Somkuti et al (1987)	Rats (F-344), 10 M per group	TPCP 100 mg/kg/day in corn oil by gavage	Exposure for 63 days. 5 animals were perfused for histopathology. The remaining animals were used for examination of testicular esterase activities, spermatid counts, motility, and morphology. Testis weight, plasma and interstitial testosterone concentration, and plasma a-tocopherol. Daily observation for neurological dysfunction or acute toxicity. Body weights were monitored weekly	–	• 25% lower testosterone values in testicular interstitial fluid • lower epididymal sperm density (+/- 50 *10^4 cells/mg cauda epididymis vs. +/- 65*10^4 cells/mg cauda epididymis in controls)
Latendresse et al. (1993)	Rats (F-344), 12 F per group	TCP 0.4 g/kg/day in sesame oil by gavage	40-day exposure and assessment of body weights, adrenal glands and ovaries	• increased adrenal gland weight (0.122 g vs. 0.054 g in controls) • cellular hypertrophy and fine cytoplasmic vacuolization of adrenocortical cells (no statistics) • inhibited adrenal neutral cholesteryl ester hydrolase (nCEH) activity (4% of controls) and ovary nCEH activity (% not indicated). • decreased adrenal ACAT activity (73% vs. 100% in controls). • elevated cholesteryl ester in adrenal glands (~20 to ~85 mg/g vs. ~20 mg/g in controls) and ovaries (~25 mg/g vs ~5 mg/g in controls). • elevated cholesterol in adrenal glands ~10 mg/g vs ~3 mg/g in controls) and ovaries (~5 mg/g vs. ~2 mg/g in controls).	• increased ovarian weights from 0(0.094 g vs. 0.072 g in controls) • cellular hypertrophy and fine cytoplasmic vacuolization of ovarian interstitial cells (no statistics) •

Table 3 Developmental toxicity study

Literature	Species	Dose/route	Experimental period/design	Maternal toxicity	Effects on development
Study report (2004)	Rats (Sprague-Dawley), 25 F per dose	TCP 20, 100, 400, 750 mg/kg/day in corn oil by gavage	EPA OPPTS 870.3700 prenatal developmental toxicity study 20-day exposure period (gestation day 0 - day 19) and assessment of body weights, ovarian and uterine examinations, foetal examinations (external malformations, soft tissue examination, skeletal examination)	*400 and 750 mg/kg/day:* • reduced overall body weight gain of 126.5 gr in 400 mg/kg/day group vs 146.6 gr in controls and 94.9 gr in 750 mg/kg/day group vs 146.6 gr in controls • lower gravid uterine weights (not quantified) *750 mg/kg/day:* • reduced food consumption (15.7 g/animal/day vs.24.1 g/animal/day in controls)	*20, 100, 400, 750 mg/kg/day:* • reduced foetal body weight (3.54 g, 3.58 g, 3.41 g, and 3.07 g, respectively) vs. controls (3.76 g) *750 mg/kg/day:* • increase in incomplete ossified bones with 100% of litters with at least one incidence versus 75% in controls

annex B

literature search strategy

PubMed

Tritolyl Phosphates + general toxicity + study types

Tritolyl Phosphates[MeSH] OR Tritolyl Phosphates[tiab] OR CAS 1330-78-5 OR Tricresyl Phosphate*[tiab]
AND
Toxicity[tiab] OR toxicogenetic*[tiab] OR toxicokinetic*[tiab] OR toxicological[tiab] OR human, biologic*[tiab] OR teratogen*[tiab] OR occupational exposure[MeSH] OR “occupational exposure* “[tiab] OR exposure, occupational[tiab] OR “adverse health effects”[tiab] OR “health damage”[tiab] OR hazard assessment[tiab] OR hazard, acute toxicity[tiab] OR “chronic toxicity”[tiab] OR “acute effects”[tiab] OR “chronic effects”[tiab] OR adme[tiab] OR absorption[MeSH] OR absorption[tiab] OR metabolism[MeSH] OR metabolism[tiab] OR distribution[tiab] OR excretion[tiab]
AND
Cohort*[tiab] OR epidemiological stud*[tiab] OR epidemiolog*[tiab] OR meta-analysis[tiab] OR meta-analyses[tiab] OR cross-sectional[tiab] OR case-control[tiab] case-cohort[tiab] OR longitudinal[tiab] OR nested case-control[tiab] OR pooled-analysis[tiab] OR pooled-analyses[tiab] OR animal study[tiab] OR animal experiment[tiab] OR laborator*[tiab] OR hospital-based[tiab] OR clinical-based[tiab]
8 hits on 15-7-2021

Tritolyl Phosphates + reproductive toxicity + study types

Tritolyl Phosphates[MeSH] OR Tritolyl Phosphates[tiab] OR CAS 1330-78-5 OR Tricresyl Phosphate*[tiab]
AND
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AND
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animal study[tiab] OR animal experiment[tiab] OR laborator*[tiab] OR hospital-based[tiab] OR clinical-based[tiab]
2 hits on 15-7-2021

Tritolyl Phosphates + study types
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AND
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19 hits on 15-7-2021

Scopus

Tritolyl Phosphates + general toxicity + study types
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AND
TITLE-ABS(Toxicity) OR TITLE-ABS(toxicogenetic*) OR TITLE-ABS(toxicokinetic*) OR TITLE-ABS(toxicological) OR TITLE-ABS(human, biologic*) OR TITLE-ABS(teratogen*) OR TITLE-ABS(“occupational exposure*“) OR TITLE-ABS(exposure, occupational) OR TITLE-ABS(“adverse health effects”) OR TITLE-ABS(“health damage”) OR TITLE-ABS(hazard assessment) OR TITLE-ABS(hazard, acute toxicity) OR TITLE-ABS(“chronic toxicity”) OR TITLE-ABS(“acute effects”) OR TITLE-ABS(“chronic effects”) OR TITLE-ABS(adme) OR TITLE-ABS(absorption) OR TITLE-ABS(metabolism) OR TITLE-ABS(distribution) OR TITLE-ABS(excretion)
AND
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8 hits on 15-7-2021

Tritolyl Phosphates + reproductive toxicity + study types
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AND
TITLE-ABS(Cohort*) OR TITLE-ABS(epidemiological stud*) OR TITLE-ABS(epidemiolog*) OR TITLE-ABS(meta-analysis) OR TITLE-ABS(meta-analyses) OR TITLE-ABS(cross-sectional) OR TITLE-ABS(case-control) OR TITLE-ABS(case-cohort) OR TITLE-ABS(longitudinal) OR TITLE-ABS(nested case-control) OR TITLE-ABS(pooled-analysis) OR TITLE-ABS(pooled-analyses) OR TITLE-ABS(animal study) OR TITLE-ABS(animal experiment) OR TITLE-ABS(laborator*) OR TITLE-ABS(hospital-based) OR TITLE-ABS(clinical-based)
3 hits on 15-7-2021

Tritolyl Phosphates + study types
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AND
TITLE-ABS(Cohort*) OR TITLE-ABS(epidemiological stud*) OR TITLE-ABS(epidemiolog*) OR TITLE-ABS(meta-analysis) OR TITLE-ABS(meta-analyses) OR TITLE-ABS(cross-sectional) OR TITLE-ABS(case-control) OR TITLE-ABS(case-cohort) OR TITLE-ABS(longitudinal) OR TITLE-ABS(nested case-control) OR TITLE-ABS(pooled-analysis) OR TITLE-ABS(pooled-analyses) OR TITLE-ABS(animal study) OR TITLE-ABS(animal experiment) OR TITLE-ABS(laborator*) OR TITLE-ABS(hospital-based) OR TITLE-ABS(clinical-based)
35 hits on 15-7-2021
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