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Environmental risk evaluation report: Cresyl diphenyl phosphate (CAS no. 26444-49-5)

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Steve Killeen

Head of Science

Executive summary

An environmental risk assessment has been carried out for cresyl diphenyl phosphate (CAS no. 26444-49-5) on the basis of available information and using the methods of a European Technical Guidance Document. This substance is mainly used in Europe as a flame retardant in textile coating, as a lubricant additive, in adhesives, in various PVC applications, in thermoset resins, in thermoplastics and in polyurethane.

Potential risks are identified for surface water (fresh and marine), sediment (fresh and marine) and soil compartments for use in PVC and polyurethane, and for use in other plastics for the marine water and sediment compartments.

Emission estimates are based on information from a number of generic sources, including emission scenario documents and other risk assessments, so they could be refined with more specific information for the substance itself. However, some of the risk characterisation ratios are high and it is unlikely that such information will be sufficient to remove all of the risks identified.

The assessment could also be refined by performing toxicity tests. The predicted no effect concentration (PNEC) for the aquatic compartment is based partly on data for other substances, and a long-term test on fish could be considered to refine the estimated value. Testing on sediment and terrestrial organisms would allow the assessments for these compartments to be refined, as the current PNECs are derived from the aquatic PNEC by equilibrium partitioning. In each case it is likely that three long-term studies would be required. The need for testing is closely linked with that for the other triaryl and alkyl/aryl phosphates considered as part of this project. A suggested testing strategy for the group as a whole is outlined in a separate overview document.

The risks to waste water treatment plant, air, secondary poisoning and for humans exposed through the environment from all uses of cresyl diphenyl phosphate are low. In addition, there is a low risk to surface water, sediment and soil for production sites, use in adhesives and lubricants, and at the regional level.

Cresyl diphenyl phosphate does not meet the criteria for a persistent, bioaccumulative and toxic (PBT) or very persistent and very bioaccumulative (vPvB) substance.

Introduction

This report is one of a series of evaluations covering a group of related substances that represent the major aryl phosphate ester products used in Europe:

Triphenyl phosphate
Trixylenyl phosphate
Tricresyl phosphate
Cresyl diphenyl phosphate
Tris(isopropylphenyl) phosphate
Isopropylphenyl diphenyl phosphate
Tertbutylphenyl diphenyl phosphate
2-Ethylhexyl diphenyl phosphate
Isodecyl diphenyl phosphate
Tetraphenyl resorcinol diphosphate

A further substance is known to be commercially available, but it has already been assessed under the Notification of New Substances (NONS) Regulations. Information is also available on some (possibly obsolete) triaryl phosphates that are not thought to be supplied in the EU. This information is summarised in Annex A, but the risks from these products have not been assessed. Information for the group as a whole has also been used in this assessment, where appropriate, to fill any gaps in the database for this particular substance. Annex B discusses the read-across of data between the various phosphate esters considered.

This group was highlighted for assessment during preliminary work for a review of flame retardants (eventually published as EA 2003), particularly because they are potential replacements for other flame retardants that have already been identified as a risk to health or the environment. Regulators need to understand the potential consequences of such market switches before substantial replacement takes place. These assessments are not intended to provide a basis for comparison between the different aryl phosphates themselves; such a comparison would require consideration of a wider range of factors than are included here (such as human health risks, efficacy, recycling potential and costs). The assessments have been produced as part of the UK Coordinated Chemical Risk Management Programme (UKCCRMP) (http://www.defra.gov.uk/environment/chemicals/ukrisk.htm).

The methodology used in the report follows that given in an EU Technical Guidance Document (TGD)[1] for risk assessment of existing substances. The scientific work was mainly carried out by the Building Research Establishment Ltd (BRE), under contract to the Environment Agency. The review of mammalian toxicity data for the assessment of non-compartment specific effects was carried out by the Institute of Environment and Health, under contract to the Department for Environment, Food and Rural Affairs (Defra).

Cresyl diphenyl phosphate has been assessed under the Organisation for Economic Cooperation and Development (OECD) Screening Initial Data Set (SIDS) programme (UNEP 2002). Data reviewed under that programme are assumed to be valid, unless newer information implies otherwise.

[1] This document has recently been replaced by similar guidance for the REACH Regulation.

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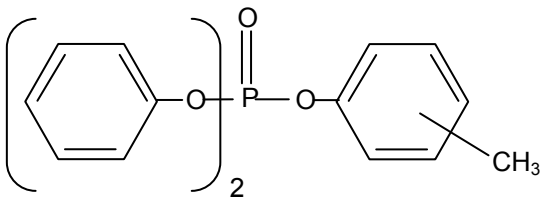
1 General substance information

1.1 Identification of the substance

This assessment considers the following commercial substance.

CAS No:	26444-49-5
EINECS No:	247-693-8
EINECS Name:	Diphenyl tolyl phosphate
Common Name:	Cresyl diphenyl phosphate
Molecular formula:	$C_{19}H_{17}O_4P$
Molecular weight:	340.32 g/mol
Structural formula:	



Other names, abbreviations, tradenames and registered trademarks for this substance include the following.

CDP
Diphenyl cresyl phosphate
Diphenyl tolyl phosphate
Methylphenyl diphenyl phosphate
Monocresyl diphenyl phosphate
Phosphoric acid, diphenyl tolyl ester
Phosphoric acid, cresyl diphenyl ester
Phosphoric acid, methylphenyl diphenyl ester
Tolyl diphenyl phosphate
Disflamoll® DPK
Kronitex® CDP
Phosflex® CDP
Santicizer® 140

Some of the tradenames and trademarks may refer to older products no longer supplied to the EU, or products produced outside the EU, but these are included in the report as they are sometimes referred to in the open literature.

The name cresyl diphenyl phosphate will be used in this assessment.

1.2 Purity/impurity, additives

1.2.1 Purity/impurities

The commercial products are mixtures containing isomers (mainly meta- and para-) of cresyl diphenyl phosphate, along with triphenyl phosphate and dicresyl phenyl phosphate (Saeger *et al.* 1979). The level of ortho-cresyl isomers in the products currently supplied is below 0.02 per cent (Bayer 2002).

Bayer (2002) reports a commercial cresyl diphenyl phosphate consisting of 25 per cent triphenyl phosphate and 5.5 per cent tricresyl phosphates and that the level of free phenolic compounds is below 0.05 per cent.

1.2.2 Additives

Additives are not thought to be present in commercially supplied products, although aryl phosphate esters are sometimes supplied as blends with other (halogenated) flame retardants.

1.3 Physico-chemical properties

Detailed test reports were not available for review, and so the validity of many of the reported values for physico-chemical properties is not always clear.

1.3.1 Physical state (at normal temperature and pressure)

The commercial products are almost colourless, clear liquids at room temperature (Bayer 2002, Great Lakes Chemical Corporation 2002).

1.3.2 Melting point

Wightman and Malalyandi (1983) reported a melting point of 37°C for pure para-cresyl diphenyl phosphate. However, the commercial products are liquid at room temperature and a melting point (pour point) of -35°C has been reported for a commercial product as determined by the ISO 3016 method (Bayer 2002). IUCLID (2000) reports a melting point (pour point) of -45 to -35°C for commercial products.

A melting/pour point of -35°C is assumed in this assessment.

1.3.3 Boiling point

Wightman and Malalyandi (1983) determined the boiling points at reduced pressure of pure isomers of cresyl diphenyl phosphate. The boiling points reported were 185°C at 0.60 mmHg (80 Pa) for ortho-cresyl diphenyl phosphate, 190°C at 0.6 mmHg (80 Pa) for meta-cresyl diphenyl phosphate and 200°C at 0.7 mmHg (93 Pa) for para-cresyl diphenyl phosphate. The paper also quoted a literature value for the boiling point of ortho-cresyl diphenyl phosphate of 260°C at 12 mmHg (1,600 Pa).

Bayer (2002) reports a boiling point of 230°C at 500 Pa for a commercial cresyl diphenyl phosphate product. The boiling point was determined by the DIN 53 171 method. IUCLID reports a similar boiling point of 225-235°C at 500 Pa for commercial products. Great Lakes Chemical Corporation (2002) report a boiling point of 300°C at 101,325 Pa for another commercial cresyl diphenyl phosphate.

Further boiling points for commercial cresyl diphenyl phosphate are reported in Boethling and Cooper (1985). The values include 368°C and 390°C, both at 760 mmHg (101, 325 Pa), 235-255°C at 4 mmHg (533 Pa) and 255°C at 5 mmHg (667 Pa).

The decomposition temperature is reported to be around 540°C and above 300°C for two commercial cresyl diphenyl phosphate products respectively (Bayer 2002, Great Lakes Chemical Corporation 2002).

A boiling point of 390°C at atmospheric pressure is assumed in this assessment.

1.3.4 Density

Bayer (2002) gives the density of a commercial cresyl diphenyl phosphate product as 1.210 g/cm^3 at 20°C determined by the DIN 51 757 method. A relative density of 1.1 at 20°C and 1.21 at 25°C is quoted for another commercial cresyl diphenyl phosphate product (Great Lakes Chemical Corporation 2002).

A relative density of 1.21 at 25°C is assumed in this assessment.

1.3.5 Vapour pressure

The vapour pressure at ambient temperature is an important physico-chemical property for environmental risk assessment because it is used to estimate both the distribution of a substance in the environment and the volatile releases from products.

No reliable data appear to be available for cresyl diphenyl phosphate at temperatures around 20-25°C. However, information on both boiling points at reduced pressure (see Section 1.3.3) and vapour pressure at elevated temperature is available.

IUCLID (2000) report a vapour pressure of 1×10^{-4} Pa at 41°C for a commercial product determined in an unpublished study. A vapour pressure of 4.7×10^{-6} mmHg (6.3×10^{-4} Pa) at 30°C is reported in Boethling and Cooper for a commercial product.

The vapour pressure or reduced pressure boiling point of a pure substance is related to the temperature within a limited temperature range according to the simplified Clapeyron-Clausius equation.

$$\log(\text{vapour pressure}) = [\underline{\Delta}H_v/2.3RT] + \text{constant}$$

where vapour pressure is in Pa
ΔH_v = heat of vapourization in J/mol
R = the universal gas constant 8.314 J/mol K
T = temperature in K

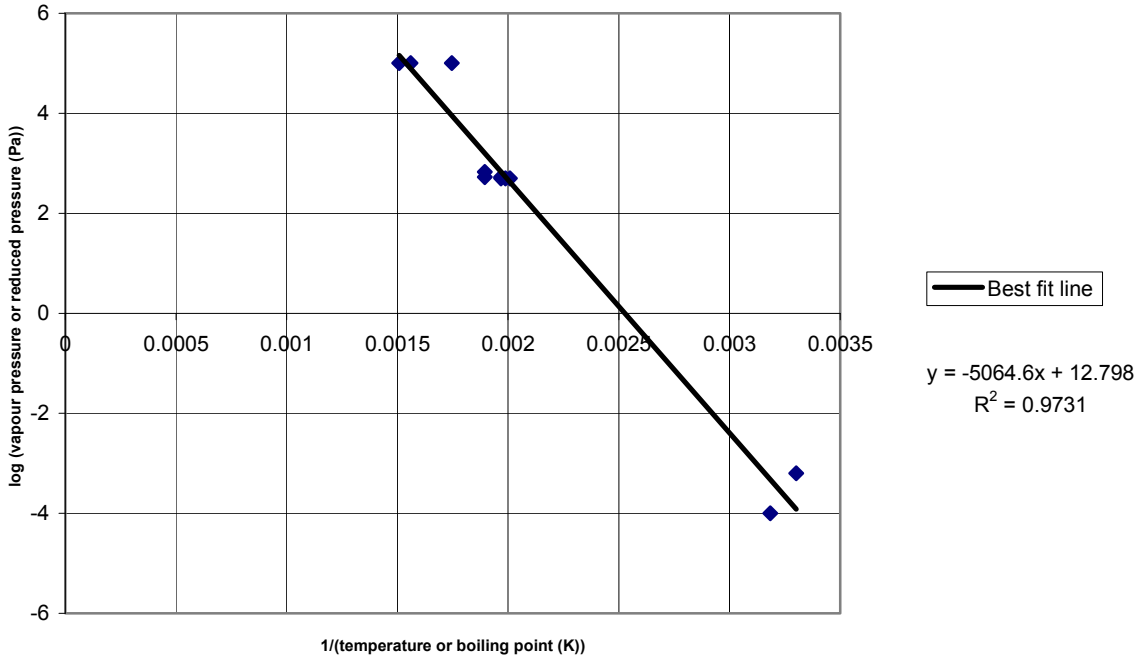
Figure 1.1 shows a plot of log (vapour pressure or reduced pressure (Pa)) against 1/(temperature or boiling point (K)) for the data available for commercial cresyl diphenyl phosphate. The following regression equation is derived from the plot.

$$\log(\text{vapour pressure (Pa)}) = [-5064.6 \times 1/(\text{temperature (K)})] + 12.798$$

The value of ΔH_v for cresyl diphenyl phosphate can be estimated as -96,846 J/mol.

Using this equation, the vapour pressure of commercial cresyl diphenyl phosphate can be estimated as 3.3×10^{-5} Pa at 20°C, 6.3×10^{-5} Pa at 25°C, 6.7 Pa at 150°C and 123 Pa at 200°C. The vapour pressure estimated at 20°C here is slightly lower than the value reported by Dobry and Keller (1957) who estimated the vapour pressure at 20°C to be 4.4×10^{-3} Pa for a purified sample of cresyl diphenyl phosphate, extrapolated from data obtained at elevated temperatures. The value for ΔH_v may vary with temperature and so could introduce further errors in extrapolating the data obtained at elevated temperatures to ambient temperatures.

Figure 1.1 Plot of log (vapour pressure or reduced pressure (Pa)) against 1/(temperature or boiling point (K)) for commercial cresyl diphenyl phosphate.



Assuming that the other cresyl diphenyl phosphates and commercial cresyl diphenyl phosphate products have a similar value for ΔH_v as estimated for ortho-cresyl diphenyl phosphate, the following vapour pressures at 20°C can be estimated using the simplified Clapeyron-Clausius equation and their respective boiling points at reduced pressure reported in Section 1.3.3.

meta-cresyl diphenyl phosphate	3.6×10^{-5} Pa at 20°C
para-cresyl diphenyl phosphate	2.5×10^{-5} Pa at 20°C
ortho-cresyl diphenyl phosphate product	4.7×10^{-4} Pa at 20°C

Pure para-cresyl diphenyl phosphate is a solid at 20°C and the estimated vapour pressure is therefore for the sub-cooled liquid.

A vapour pressure (at 25°C) of 1.04×10^{-7} mmHg (1.4×10^{-5} Pa) can be estimated for cresyl diphenyl phosphate from its structure using the Syracuse Research Corporation MPBPWIN (version 1.28) software (modified Grain method). Boethling and Cooper (1985) estimated a vapour pressure at 25°C of 2.1×10^{-6} to 4.1×10^{-5} mmHg (2.8×10^{-4} to 5.5×10^{-3} Pa) from the boiling point of commercial cresyl diphenyl phosphate (Grain method).

A vapour pressure of 3.3×10^{-5} Pa at 20°C or 6.3×10^{-5} Pa at 25°C (as derived by the above analysis of available data for the commercial product) is assumed in this assessment for commercial cresyl diphenyl phosphate.

1.3.6 Water solubility

Saeger *et al.* (1979) determined the solubility of a commercial cresyl diphenyl phosphate using a shake flask method. The substance used was a commercial product consisting of a mixture of isomers of cresyl diphenyl phosphate along with triphenyl phosphate and dicresyl phenyl phosphates. In the experiment, 25 ml of the phosphate ester was added to 500 ml of purified water and shaken for 48 hours. The solution was then allowed to stand for one week in the dark before the aqueous phase was centrifuged at 20,000 g for one hour to remove droplets of undissolved substance. The aqueous phase was then extracted twice with methylene dichloride and the extracts were analysed for the commercial product by a gas chromatography method (the centrifugation/extraction and analysis steps were carried out in duplicate and gave a mean relative average deviation of 13 per cent). The solubility of the substance tested (as the commercial product) was determined to be 2.6 mg/l at room temperature. The composition of the saturated solution was found to be different to that of the commercial product, with the proportion of triphenyl phosphate elevated in solution compared with that in the commercial product. This indicates a preferential dissolution of the triphenyl phosphate component (water solubility of triphenyl phosphate itself was determined as 1.9 mg/l). As the solubility determined of 2.6 mg/l was based on the total concentration of all components of the commercial product, the actual solubility of the cresyl diphenyl phosphate may be lower than indicated by this figure.

A water solubility of around 0.23 mg/l can be estimated for cresyl diphenyl phosphate using the Syracuse Research Corporation WSKOW version 1.30 software (the estimate is based on a log K_{ow} of 5.25).

A water solubility of 2.6 mg/l is assumed in this assessment for cresyl diphenyl phosphate as representative of the commercial material.

1.3.7 Octanol-water partition coefficient (log K_{ow})

The octanol-water partition coefficient of a commercial cresyl diphenyl phosphate was determined using a shake flask method (Saeger *et al.* 1979). The substance used was a commercial product consisting of a mixture of cresyl diphenyl phosphate along with triphenyl phosphate and dicresyl phenyl phosphate. In the study, the substance was dissolved in n-octanol (at least two concentrations were tested between 100 mg/kg and 10,000 mg/kg) and 100 ml of this solution was shaken with 500 ml of purified water for 48 hours in the dark. The mixture was then allowed to stand for seven days in the dark before the concentration in the water phase (based on the sum of the major components of the product found in the gas chromatography trace) was determined (as only small amounts of the test substance were found to partition into the water phase, the concentration of the substance in the n-octanol phase was taken to be the starting concentration). The log K_{ow} obtained was determined to be 32,000 (log K_{ow} = 4.51).

Renberg *et al.* (1980) determined the octanol-water partition coefficient for a cresyl diphenyl phosphate (the same substance as used by Saeger *et al.* 1979 above) using a high performance thin layer chromatography (HPTLC) method. Three main components of the commercial product were evident using the method and the partition coefficients determined (log values) for these components were 3.23, 3.63 and 4.06. The mean value obtained for all components was 3.77. The component giving rise to the log K_{ow} value of 3.23 was tentatively identified as triphenyl phosphate (the log K_{ow}

value for triphenyl phosphate itself was determined as 3.15 using the HPTLC method). These measured values are in reasonable agreement with the values estimated above.

A log K_{ow} value of 4.4 has been reported for cresyl diphenyl phosphate (Bengtsson *et al.* 1986). The value was from an unpublished source.

A log K_{ow} of 5.24 can be estimated for cresyl diphenyl phosphate from its structure using the Syracuse Research Corporation Log K_{ow} (version 1.60) software.

A log K_{ow} of 4.51, based on the measured data of Saeger *et al.* (1979), is used in the assessment.

1.3.8 Hazardous physico-chemical properties

Bayer (2002) gives a flash point (open cup) of above 230°C for a commercial cresyl diphenyl phosphate determined by the ISO 2592 method. A similar flash point of above 220°C is given for another commercial cresyl diphenyl phosphate product. IUCLID (2000) report a flash point (closed cup) of above 242°C for commercial products.

Bayer (2002) reports the ignition temperature as above 500°C for a commercial cresyl diphenyl phosphate determined by the DIN 51794 method.

No information could be located for explosivity or oxidising properties of this substance.

1.3.9 Henry's law constant

A Henry's law constant of 4.39×10^{-8} atm m^3/mol (0.0044 Pa m^3/mol) at 25°C can be estimated for cresyl diphenyl phosphate from chemical structure (bond contribution method) using the Syracuse Research Corporation HENRYWIN (version 3.00) software.

A further Henry's law constant for cresyl diphenyl phosphate can be estimated from the vapour pressure of 3.3×10^{-5} Pa at 20°C or 6.3×10^{-5} Pa at 25°C (see Section 1.3.5) and the water solubility of 2.6 mg/l at room temperature (see Section 1.3.6). Using these data, the Henry's law constant can be calculated as 4.3×10^{-3} Pa m^3/mol at 20°C or 8.2×10^{-3} Pa m^3/mol at 25°C, which is very close to the value estimated using the HENRYWIN software. These values are used in this assessment as they are consistent with the vapour pressure and water solubility data used in this assessment.

1.3.10 Summary of physico-chemical properties

The physico-chemical properties of cresyl diphenyl phosphate are summarised in Table 1.1. Most of the data have been obtained with the commercial products and so some of the properties may vary depending on the actual composition of the product.

For the purposes of this assessment, the commercial substance is considered to behave as a single substance in the environment, even though it is a complex mixture.

Table 1.1 Summary of environmentally relevant physico-chemical properties for cresyl diphenyl phosphate

Property	Value
Melting point	-35°C (pour point)
Boiling point (at atmospheric pressure)	390°C at 101,325 Pa
Relative density	1.21 at 25°C
Vapour pressure	3.3×10^{-5} Pa at 20°C or 6.3×10^{-5} Pa at 25°C
Water solubility	2.6 mg/l at room temperature
Octanol-water partition coefficient (log value)	4.51
Henry's law constant	4.3×10^{-3} Pa m^3/mol at 20°C or 8.2×10^{-3} Pa m^3/mol at 25°C

2 General information on exposure

2.1 Production

There are two known European production sites (including Chemtura (formerly Great Lakes), UK) and one additional European supplier. Information on production volume and market size is therefore confidential. It is possible that other companies may supply this substance, but no further information is available for this report.

2.2 Use

2.2.1 General introduction

Triaryl phosphate flame retardants were first commercialised in the early twentieth century for use in flammable plastics such as cellulose nitrate and later for cellulose acetate (Weil 1993). Use in cellulose products is still significant, but the largest application is now in plasticized vinyl polymers. The main applications of these products are in wire and cable insulation, connectors, automotive interiors, vinyl moisture barriers, furniture upholstery, conveyor belts (for mining) and vinyl foams.

In addition to their use as flame retardants in polymer systems, triaryl phosphates are also used as flame retardant hydraulic fluids, lubricants and lubricant additives (Weil 1993). Small amounts are also reported to be used as non-flammable dispersing media for peroxide catalysts.

2.2.2 Uses of cresyl diphenyl phosphate

The main area of use of cresyl diphenyl phosphate, especially in Europe, is as a flame retardant in vinyl polymers and in acrylonitrile-styrene-butadiene (ABS) blends (Weil 1993).

Information on the sales of cresyl diphenyl phosphate in the EU has been provided by the relevant supplier companies for the year 2005. The specific figures are confidential; however, major current areas of use of cresyl diphenyl phosphate include use in textile coating, as a lubricant additive, in adhesives, in various PVC applications, in thermoset resins, in thermoplastics and in polyurethane.

3 Environmental exposure

This assessment has been prepared in accordance with the principles of Council Regulation (EEC) 793/93 (the Existing Substances Regulation or ESR)[2] and the methods laid down in Commission Regulation (EC) 1488/94[3], which is supported by a technical guidance document or 'TGD' (EC 2003). The European Union System for the Evaluation of Substances (EUSES) computer program[4] (v2.0.3) implements the TGD models. The EUSES output file for this assessment is confidential because of the information it contains on tonnage and use pattern.

The assessment is generic, representing a *realistic worst case approach* for a hypothetical environment that broadly reflects average European conditions. It uses a number of assumptions (such as a fixed river dilution level), and further details can be found in the TGD. The assessment is based on estimated sales figures for Europe and some site-specific information. Since these are confidential, the calculations are presented in the Confidential Annex, but they are discussed qualitatively in the report as appropriate.

3.1 Environmental fate and distribution

3.1.1 Environmental degradation

Abiotic degradation

Atmospheric photooxidation

A rate constant for reaction of cresyl diphenyl phosphate with atmospheric hydroxyl radicals of 1.2×10^{-11} cm^3/molecule s can be estimated from its structure using the Syracuse Research Corporation AOP (version 1.86) software. This program implements the method recommended in the TGD for estimating the rate constant.

Using an atmospheric hydroxyl radical concentration of 5×10^5 molecules/cm^3, a half-life for the reaction in air can be estimated as 32 hours.

Hydrolysis

The hydrolysis of a commercial cresyl diphenyl phosphate product in natural water (Lake Ontario (pH 8.2)) has been studied by Howard and Deo (1979). Saturated solutions of the test substances were prepared by shaking an excess of the substance with the natural water for two hours, followed by filtration (11 μm) to remove the undissolved material. The concentration of the cresyl diphenyl phosphate in the solution was then determined, the solution was incubated at 21°C and the concentration of the test substance present was determined at various time periods. The experiments all showed a lag period of around two days prior to the onset of degradation of the cresyl diphenyl phosphate. After this lag phase, the substance was found to degrade rapidly within five to six days. Given the initial lag phase prior to degradation, microbial degradation rather than hydrolysis was probably the dominant

[2] O.J. No L 084, 05/04/1993 p. 0001–0075.
[3] O.J. No L 161, 29/06/1994 p. 0003–0011.
[4] Available from the European Chemicals Bureau, http://ecb.jrc.ec.europa.eu/.

process in these samples (although the water samples were filtered prior to use, the size of the filter (11 μm) was chosen so as not to remove microorganisms).

Great Lakes Chemical Corporation (2003) indicate that hydrolysis of aryl phosphates can also occur under acidic conditions and packages are usually added to hydraulic fluids to delay the onset of hydrolysis during the service life of the products. The standard test for such fluids is the 'coke bottle' test. In this test, the fluid is placed in a coke bottle with distilled water (sometimes with catalytic metals such as copper) and the degradation is followed by an increase in acidity (the initial hydrolysis product would be diaryl phosphates (diesters of phosphoric acid), which are acidic). The rate of hydrolysis in such tests generally increases as the acidity increases during the test. However, although this indicates that hydrolysis of aryl phosphates can occur at acidic pHs, the autocatalysis seen in the test as a result of the formation of acidic products (resulting in an increase in acidity) is unlikely to occur in the environment owing to its natural buffering capacity.

Photolysis

No data are available on the direct photolysis reactions of cresyl diphenyl phosphate under environmentally relevant conditions.

Biodegradation

IUCLID (2000) and Bayer (2002) report the results of an unpublished OECD 301C Modified MITI ready biodegradation test for a commercial cresyl diphenyl phosphate. The inoculum used was predominantly domestic sewage and the degradation seen was 75 per cent after 28 days related to oxygen consumption. The results of this test indicate that the substance can be considered to be readily biodegradable.

Saeger *et al*. (1979) determined the biodegradation of a commercial cresyl diphenyl phosphate using various test systems. The substance used was a commercial product consisting of a mixture of isomers of cresyl diphenyl phosphate along with triphenyl phosphate and dicresyl phenyl phosphate. The first test investigated the primary degradation of the test substance using a river die-away method. The water used in the test was settled Mississippi River water. The test substance (at a concentration of one mg/l) was added to the water and the test vessels (bottles) were sealed with a foil-lined cap and stored in the dark at room temperature. Sterile control solutions (containing the same concentration of test substance) and positive control solutions (containing linear alkyl benzene sulphonate) were also run. At various times during the study, a bottle was removed and the amount of phosphate ester present was determined (by a gas chromatographic method that analysed the sum of major components in the test substance). The results showed that the test substance underwent primary degradation in the test system, with complete degradation in less than seven days. No significant degradation was seen in the sterile controls.

The second part of the study investigated primary degradation of the test substance using a semi-continuous activated sludge (SCAS) unit. The method used was based on the Soap and Detergent Association procedure (Soap and Detergent Association 1965 and 1969). The activated sludge used in the test was of domestic origin and the vessels used in the test had an operating volume of 1.5 litres. The test substance was added to the unit at a rate of 3 mg/l per 24-hour cycle. The units were operated for a period of 22 weeks, where samples of the mixed liquor were removed at weekly intervals and the concentration of the phosphate ester determined. The results indicated an equilibrium removal rate of 82 ± 12 per cent in the test system. To investigate the loss by volatilisation, the off-gases were passed through a series of

scrubbers. No significant loss by volatilisation (less than 0.5 per cent per cycle) of the phosphate ester was seen in the experiment.

The final part of the study investigated the ultimate mineralisation of the test substance using a degradation method based on the modified Sturm method. An acclimated bacterial seed was prepared by incubation of 100 ml of settled supernatant from a SCAS unit with 20 mg of one of eleven phosphate esters (including the test substance), 50 mg of yeast extract and 900 ml of standard biological oxygen demand (BOD) water for 14 days in the dark at room temperature. At the end of the incubation period, a combined acclimated seed was prepared by mixing samples from each acclimation bottle and this was used as seed for the inherent biodegradation test. In the test 500 ml of the composite seed was added to 5,500 ml of BOD water and the substance was then added to the bottle (initial concentration 23.1 mg/l). During the test, CO_2-free air was continually bubbled through each bottle and the CO_2 evolved from the system was determined. Control bottles (receiving no test substance) were also run. The amount of CO_2 evolved from the control bottles was around 10-15 per cent of that of the bottles containing the test substance and the results were corrected for this background CO_2 level. The CO_2 evolved from the test substance (expressed as a percentage of the maximum theoretical amount) was 53 per cent after seven days, 84 per cent after 28 days and 91 per cent after 48 days. Therefore, the substance can be considered at least inherently biodegradable based on the results of this test.

Boethling and Cooper (1985) indicate that unpublished work by Shelton and Tiedje (1981) found no evidence for biodegradation of cresyl diphenyl phosphate under anaerobic conditions over eight weeks using 1:10 dilutions of primary anaerobic sludge. The method used determined the amount of methane formed in the system. Information on this study is limited.

Summary of degradation

Abiotic degradation

There is no reliable information on the rate of hydrolysis of cresyl diphenyl phosphate. By comparison with other triaryl phosphates (for example, see risk evaluation report for triphenyl phosphate in this series) hydrolysis would be expected to occur, especially at pHs above nine. Boethling and Cooper (1985) suggested that the hydrolysis rates for triaryl phosphates containing alkyl substituents on the aromatic ring should be lower than those for triphenyl phosphate due to the electron-donating character of these groups. Since pH in the environment is generally lower than that where significant hydrolysis of triphenyl phosphate may be expected to occur (hydrolysis appears to be rapid at pHs above eight, but slow at neutral pH, although the rate may again increase with decreasing pH) and the rate of hydrolysis of cresyl diphenyl phosphate is expected to be slower than that for triphenyl phosphate, the rate of hydrolysis is assumed to be zero in this assessment. However, in some acidic or alkaline environments, hydrolysis could become significant and so the effect of inclusion of a hydrolysis rate on the predicted concentrations is considered in Annex C.

No studies are available on the direct photolysis reactions of cresyl diphenyl phosphate under environmentally relevant conditions. The rate of this reaction is assumed to be zero in the assessment.

Atmospheric photooxidation of cresyl diphenyl phosphate is predicted to occur with a half-life of around 32 hours. This reaction is taken into account in the risk assessment.

In summary, the abiotic degradation rate constants and half-lives assumed in the assessment are as follows:

Hydrolysis	$khydr_{water}$ = 0 d^{-1}	half-life = infinite
Photolysis	$kphoto_{water}$ = 0 d^{-1}	half-life = infinite
Atmospheric photooxidation	k_{OH} = 1.2×10^{-11} cm^3/molecule s	half-life = 32.1 h.

Biodegradation

The most likely pathway for biodegradation of aryl phosphates is initial hydrolysis of the phosphate ester to form orthophosphate and the corresponding phenolic compounds or alcohols, which then themselves undergo further biodegradation (Saeger *et al.* 1979).

The available biodegradation information for cresyl diphenyl phosphate indicates that it can be considered to be readily biodegradable (no information on the 10-day window).

The recommended biodegradation half-lives for surface water and soil from the TGD for cresyl diphenyl phosphate (assuming it is readily biodegradable but not meeting the 10-day window) are summarised below:

Sewage treatment plant	k = 0.3 h^{-1}	half-life = 2.3 hours
Surface water	k = 1.4×10^{-2} d^{-1}	half-life = 50 days
Sediment	k = 7.7×10^{-3} d^{-1}	half-life = 90 days
Soil	k = 7.7×10^{-3} d^{-1}	half-life = 90 days

These values are used in the risk assessment.

The available screening studies with which to compare these data are limited and have generally measured primary degradation rather than mineralisation. However, available river die-away studies generally show rapid primary degradation (half-life less than seven days). The intermediate products of primary degradation are likely to be phenol and cresol, which are themselves likely to undergo rapid mineralization.

For sediment, the TGD recommends that the default rate constant should be ten times lower than that for soil to reflect the fact that the deeper sediment layers are anaerobic (this calculation assumes that degradation under anaerobic conditions does not occur). However, the available information for some other triaryl phosphates (for example, see the risk evaluation report for triphenyl phosphate in this series) suggests that these substances may also be degraded under anaerobic conditions at a similar rate to aerobic conditions. Therefore, for this assessment, it is assumed that the degradation rate constant (and hence half-life) in sediment will be the same as in soil.

Although the phenolic part of the triaryl phosphate will undergo mineralisation, orthophosphate/phosphoric acid will also be produced as a result of the degradation. The fate, behaviour and effects of this substance are beyond the scope of this assessment.

3.1.2 Environmental partitioning

Adsorption

No experimental sediment or soil adsorption data are available for cresyl diphenyl phosphate.

A K_{oc} value of 8,659 l/kg can be estimated for cresyl diphenyl phosphate from its structure using the Syracuse Research Corporation PCKOC version 1.63 software using a molecular connectivity index method.

Chapter 4 of the TGD recommends the following equation for estimating K_{oc} from log K_{ow} for phosphates:

$$\log K_{oc} = 0.49 \log K_{ow} + 1.17$$

Using this equation for triphenyl phosphate (log K_{ow} of 4.51) results in an estimated K_{oc} of 2,398 l/kg. As this value is derived using the method recommended in the TGD, it is used in this risk assessment. The resulting partition coefficients for soils and sediment calculated using the methods given in the TGD are shown below.

K_{oc}	2,398 l/kg		
Kp_{susp}	240 l/kg	$K_{susp\text{-}water}$	61 m^3/m^3
Kp_{sed}	120 l/kg	$K_{sed\text{-}water}$	61 m^3/m^3
Kp_{soil}	48 l/kg	$K_{soil\text{-}water}$	72 m^3/m^3

These values are used in this risk assessment.

Volatilisation

No studies on the volatilisation of cresyl diphenyl phosphate appear to be available. Henry's law constant estimated for cresyl diphenyl phosphate is 8.2×10^{-3} Pa m^3/mol at 25°C. This indicates that volatilisation from water is likely to be limited.

Fugacity modelling

The potential environmental distribution of cresyl diphenyl phosphate has been studied using a generic level III fugacity model. The model used was a four-compartment model (EQC version 1.01, May 1997) that has been circulated for use within the Organisation for Economic Cooperation and Development (OECD) High Production Volume (HPV) programme. The model was run four times with a nominal release rate of 1,000 kg/hour initially entering the air, soil or water compartments in different proportions. The physico-chemical properties used and the results of the modelling exercise are shown in Table 3.1.

The results of the model show that only a small amount of the cresyl diphenyl phosphate released to the environment will be in the air compartment at steady state. When the substance is released to air it distributes mainly to the soil compartment, presumably by atmospheric deposition. When it is released to soil, the substance generally remains in the soil, with only a small fraction distributing to the water and sediment compartment. When released to water, the substance is likely to distribute to the water and sediment phase at steady state.

The behaviour of cresyl diphenyl phosphate during waste water treatment was estimated using the EUSES model. Using a degradation rate constant of 0.3 h^{-1} (see Section 3.1.1), a K_{oc} of 2,398 l/kg (see above) and a vapour pressure of 6.3×10^{-5} Pa at 25°C (see Section 1.3.5), the following behaviour is predicted:

Degraded	54.4%
Adsorbed to sludge	18.5%
Volatilised to air	5.2×10^{-3}%
To effluent	27.0%

These values are used in the predicted environment concentration (PEC) calculations.

Table 3.1 Results of generic level III fugacity model for cresyl diphenyl phosphate

Input data	Value				
Vapour pressure	3.3×10^{-5} Pa at 20°C				
Water solubility	2.6 mg/l				
Henry's law constant	0.21 at 20°C				
Log K_{ow}	4.51				
Atmospheric half-life	32.1 hours				
Half-life in water	50 days				
Half-life in soil and sediment	90 days				
Emission rate	**Model results at steady state**				
	Amount in air	**Amount in soil**	**Amount in water**	**Amount in sediment**	**Overall residence time/persistence**
1,000 kg/hour to air 1,000 kg/hour to soil 1,000 kg/hour to water	0.27%	84.8%	11.7%	3.24%	75.4 days
1,000 kg/hour to air 0 kg/hour to soil 0 kg/hour to water	0.95%	96.3%	2.14%	0.59%	64.6 days
0 kg/hour to air 1,000 kg/hour to soil 0 kg/hour to water	1.1×10^{-4}%	99.9%	0.053%	0.015%	130 days
0 kg/hour to air 0 kg/hour to soil 1,000 kg/hour to water	5.0×10^{-4}%	0.051%	78.2%	21.7%	31.8 days

3.1.3 Bioaccumulation and metabolism

Measured data

Uptake from water

The bioconcentration of a commercial triaryl phosphate product in bleak (*Alburnus alburnus*) was investigated by Bengtsson *et al.* (1986). The test substance contained triphenyl phosphate, cresyl diphenyl phosphate (two main components), tricresyl phosphate (three main components) and trixylenyl phosphate (three main components). A quantitative composition was not included. The tests were carried out using a flow-though system with natural brackish water (7‰ salinity) at 10°C. The fish used in the test had an average weight of five grams (53 fish were used in 60 litres of water) and were fed twice daily (once daily at weekends) with a 0.25 g portion of commercial food. The pH of the water was 7.6-7.9 and the dissolved oxygen concentration remained above 90 per cent of saturation throughout the study. The experiment consisted of a 14-day uptake period where the fish were exposed to a nominal concentration of 50 μg/l of the triaryl phosphate product, followed by a 14-day depuration period in clean flowing water. Samples of both fish (three fish per sample time except at day 14 and 28 where five groups of three fish were sampled) and water were analysed for the concentrations of the main components (as determined by gas chromatographic analysis) of the triaryl phosphate product on days 0, 1, 2, 4, 7, 14, 17, 18, 21 and 28 of the experiment. No mortality or abnormal behaviour was seen in the fish during the experiment. Steady state was found to have been reached within the

14-day exposure period (steady state was actually attained within two days) for triphenyl phosphate, the cresyl diphenyl phosphate components and two of the tricresyl phosphate components of the mixture. The steady-state bioconcentration factors (BCF) were determined as 400 l/kg, 100-220 l/kg and 800 l/kg for these components respectively. For the other components, steady state was approached, but had not been reached by the end of the 14-day uptake period and the non-steady state BCFs estimated at 14 days were 400 l/kg for the remaining tricresyl phosphate component and 1,300-1,900 l/kg for the three trixylenyl phosphate components. All components were found to be rapidly eliminated from the fish, with a depuration half-life of four days or less. The triphenyl phosphate, cresyl diphenyl phosphate and tricresyl phosphate components were almost completely eliminated from the fish within 14 days but the trixylenyl phosphate components were still evident in the fish after 14 days.

Uptake from food

A long-term dietary accumulation study with a commercial triaryl phosphate product (Pliabrac 521) was carried out with minnows (*Phoxinus phoxinus*) (Bengtsson *et al.* 1986). The substance tested contained triphenyl phosphate, cresyl diphenyl phosphate (two main components), tricresyl phosphate (three main components) and trixylenyl phosphate (three main components). A quantitative composition was not included. The test was carried out using a flow-through system with six groups of 30 fish (average bodyweight 1.9 g), each in 50 litres of natural brackish water (7‰ salinity). The test was started in January and was carried out for 163 days (although the resulting concentrations in fish were determined after four months only) and the water temperature followed the natural seasonal fluctuations (3.6 to 4.5°C from January to April, 7°C by the end of April, 13°C by the end of May and 12.3 to 15.5°C from June until the end of the experiment). The dissolved oxygen concentration in the test was always above 90 per cent of saturation and the pH of the water was 7.7-8.0. Five concentrations of the test substance were used (100, 300, 1,000, 3,000 and 10,000 mg/kg food) and a control using uncontaminated food was run. The food used was a commercial fish food which was spiked by adding the triaryl phosphate as a solution in acetone and evaporating off the solvent. The fish were given two 0.25 g portions of food per day. The total amount of food given to the fish by four months of the experiment was two grams per fish. No mortalities or abnormal behaviour were seen in any of the fish, and all food given to the fish was eaten. The concentrations of the various components of the fish after four months exposure are shown in Table 3.2. Overall, only around 0.017 to 0.14 per cent of the total amount of the test substance fed to fish was found to be present in the fish at the end of the study. The bioaccumulation factors, based on the estimated concentration in fish and the concentration in food, are all very much less than one.

Table 3.2 Concentrations in minnows after four months exposure to contaminated food

Food concentration	Total concentration in fish (mg/kg fresh weight)			
	Triphenyl phosphate	Cresyl diphenyl phosphate (sum of two components)	Tricresyl phosphate (sum of three components)	Trixylenyl phosphate (sum of 3 components)
Control	0.005	Not detected	0.005	Not detected
100 mg/kg	0.030	0.023	0.053	0.094
300 mg/kg	0.020	0.016	0.085	0.47
1,000 mg/kg	0.225	0.019	0.225	0.896
3,000 mg/kg	0.12	0.016	0.88	2.01
10,000 mg/kg	0.73	0.043	1.39	2.05

Calculated data

For the terrestrial food chain, the TGD requires a BCF for earthworms. No experimental data are available for this endpoint and so an earthworm BCF can be estimated using the following equation given in the TGD:

$$BCF_{earthworm} = 0.84 + 0.012\ K_{ow} / RHO_{earthworm}$$

Where $RHO_{earthworm}$ = density of the earthworm = 1 kg/l.
K_{ow} = octanol-water partition coefficient.

Using a log K_{ow} value of 4.51, the $BCF_{earthworm}$ is estimated as 389. This value is used in this assessment, although the reliability of this estimate is unknown.

Summary of accumulation

One fish bioconcentration study is available for cresyl diphenyl phosphate. This showed a steady-state BCF of 100-200 l/kg for the cresyl diphenyl phosphate component of a commercial product, based on parent compound analysis.

The log K_{ow} value for cresyl diphenyl phosphate is 4.51. Using the methods recommended in the TGD, a BCF for fish of 1,360 l/kg. This value is much higher than the value obtained experimentally.

A BCF of 200 l/kg based on the experimental data is assumed in this risk assessment for cresyl diphenyl phosphate.

In addition to a BCF, the revised TGD also requires a biomagnification factor (BMF) to be taken into account. For cresyl diphenyl phosphate, the default BMF would be one based on the BCF value determined above. This is consistent with the available feeding study data that showed that bioaccumulation from food was low.

Using a log K_{ow} value of 4.51 and the methods recommended in the TGD, the $BCF_{earthworm}$ is estimated as 389.

3.2 Environmental releases

3.2.1 General discussion

Releases from the production and use of cresyl diphenyl phosphate were estimated using a number of sources such as the default methods from the TGD, the Emission Scenario Document (ESD) on plastics additives (OECD 2004a) the Emission Scenario Document on lubricants (OECD 2004b) and scenarios developed under the Existing Substances Regulation for other substances with similar uses. In the absence of specific information on the substance, ESDs and scenarios for other substances are considered to be a reasonable basis for emission estimation; the TGD default values are intended for use as realistic worst case values in the absence of other data. Hence, estimates from these sources will have some degree of uncertainty. Actual calculations are confidential, as they are based on confidential production and use figures.

The producers of cresyl diphenyl phosphate provided information on the amounts used by representative large customers, and this was used in local estimates of emissions from use. Some additional information on waste treatment and cleaning at a small number of user sites was also provided; this information did not contradict the assumptions made on the basis of the ESD on plastics additives.

3.2.2 Releases from production

Releases from production sites were estimated from specific information provided by the producing companies. The results are included in Table 3.4.

3.2.3 Releases from use (processing)

PVC

Emissions from the use in PVC were estimated using the methods outlined in the ESD on plastics additives (OECD 2004a). The ESD provides methods for estimating the releases from three stages:

- handling of raw materials;
- compounding – the blending into the polymer of additives;
- conversion – the forming of the polymer into finished articles.

The first two stages are assumed to always take place together. There are companies which compound the plastics and then sell them on to converters, so separate calculations are carried out for the two as well as for the case where compounding and conversion take place together. Emission factors in the ESD are derived from information on a model substance, di(2-diethylhexyl)phthalate (DEHP), and are modified according to the relative properties of this substance and the substance of interest. The main property affecting the emissions is the vapour pressure of the substance. Cresyl diphenyl phosphate has a similar vapour pressure to that of DEHP at the processing temperatures, and is classed as of 'medium volatility' according to the criteria in the ESD[5]. The ESD also uses the particle size or form of the substance in

[5] 'Medium volatility' is used in comparison to DEHP which is of 'medium volatility'. All phosphates in this series have vapour pressures considered low for organic substances.

estimating the possible releases from raw materials handling. Cresyl diphenyl phosphate is a liquid (Section 0).

The emission factors derived using the ESD methods depend on the type of PVC product, and are:

- Compounding (including raw materials handling): 0.005-0.01 per cent to air, 0-0.015 per cent to waste water.
- Conversion: 0.005-0.025 per cent to air, 0.005-0.025 per cent to waste water.

Thermoplastics, thermosets and polyurethane

The methods from the ESD are also used for these polymeric materials. For these the emission factors are:

- Compounding (including raw materials handling): 0.005 per cent to air, 0.015 per cent to waste water.
- Conversion: 0.005 per cent to air, 0.005 per cent to waste water.

Textiles

The use of cresyl diphenyl phosphate in textiles is in coatings for PVC fabrics, and as such can be considered to be a plastics process. The ESD on plastics additives (OECD 2004a) provides information on release factors for this use and these are used in the assessment. The emission factors used are:

- Compounding (including raw materials handling): 0.01 per cent to water.
- Conversion: 0.025 per cent to air, 0.025 per cent to water.

Lubricants

Emissions from the use of the substance in lubricants (from the blending step) were estimated using the methods outlined in the ESD on lubricants (OECD 2004b). Estimates were made for use as an additive in lubricants. The estimated emissions to air from lubricant blending are very low. The emission factor for releases to water from blending is 4.5×10^{-5} kg/tonne lubricant.

Adhesives

Information from risk assessments on other substances was used to estimate the emissions from formulation into adhesives. These are considered to be negligible.

3.2.4 Releases over lifetime of products

Cresyl diphenyl phosphate is used in products which are likely to have extended service lives (more than one year). These are therefore potentially important sources of emission.

Releases from the service life of lubricants are estimated using the methods in the ESD (OECD 2004b). Use in automotive lubricants is assumed.

Possible losses from PVC and other polymeric materials through leaching and volatilisation are also considered in this section. Limited information on the release of cresyl diphenyl phosphate is available, and has been included here, but estimates are based on the methods outlined in the Emission Scenario Document (OECD 2004a) and also take into account the approaches used in the risk assessment of other substances (for example, the risk assessment on medium-chain chlorinated paraffins carried out under the Existing Substances Regulation (ECB 2005)). The approach taken also considers the release of polymer particulates (waste remaining in the environment) over the lifetime of products and at disposal as appropriate; this is based on the treatment of this area in other risk assessments such as that on medium-chain chlorinated paraffins.

Leaching loss

No information was found on the leaching potential of cresyl diphenyl phosphate from articles. Factors from the ESD on plastics additives are used in the assessment for emissions from PVC products. Compared to the model substance DEHP in the ESD, cresyl diphenyl phosphate is classed as a high solubility substance, and so the factors are increased to account for this. The factors are zero to 0.5 per cent over the lifetime of the product for indoor use, depending on the type of product, and up to 14 per cent for outdoor use depending on the duration of the service life.

The ESD is also used to estimate release from use in thermoset plastics and textiles. The factor used is 0.5 per cent over the lifetime of the product.

Losses from adhesives in their service life are also estimated using the ESD, and assuming the equivalent of outdoor use.

Polyurethane articles are thought not to come into contact with water on a regular basis and so emissions to water from these uses are considered to be negligible.

Volatile loss

The stability of, and volatile loss from, several commercial aryl and alkyl/aryl phosphate products has been studied using a combination of differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) under a nitrogen atmosphere (Shankwalkar and Cruz 1994) and an oxygen atmosphere (Shankwalkar and Placek 1992). The results of the studies are summarised in

Table 3.3.

The results under a nitrogen atmosphere show that the triaryl phosphates start to decompose at temperatures of around 310-350°C, whereas alkyl diphenyl phosphates tested start to decompose at around 260°C. The decomposition temperatures under an oxygen atmosphere are significantly lower. For all the substances tested, significant weight loss occurred at temperatures below that at which decomposition begins, indicating a loss of the substance by volatilisation at elevated temperatures.

Table 3.3 Thermal degradation temperature and weight loss of aryl and alkyl/aryl phosphates

Phosphate ester	Experiments under an oxygen atmosphere				Experiments under a nitrogen atmosphere		
	Start of thermal degradation	1% weight loss	5% weight loss	10% weight loss	Start of thermal degradation	5% weight loss	10% weight loss
Triphenyl phosphate	>400°C	188°C	236°C	252°C			
Tricresyl phosphate	215°C	184°C	255°C	252°C	333°C	272°C	306°C
Trixylenyl phosphate	210°C	224°C	268°C	286°C	311°C	276°C	302°C
Isopropyl phenyl diphenyl phosphate[a]	210-215°C	200-218°C	239-265°C	263-288°C	311-314°C	264-282°C	293-307°C
Tertbutyl phenyl diphenyl phosphate[a]	295-305°C	213-234°C	262-277°C	280-295°C	338-347°C	274-278°C	305-306°C
2-Ethylhexyl diphenyl phosphate	200°C	90°C	220°C	229°C	257°C	226°C	231°C
Isodecyl diphenyl phosphate	165°C	93°C	213°C	235°C	264°C	233°C	246°C

Notes: a) Data for three (nitrogen atmosphere) or four (oxygen atmosphere) different grades.

Although cresyl diphenyl phosphate itself was not studied in this test, it is likely that this substance will behave in a similar fashion to the other triaryl phosphates.

Great Lakes Chemical Corporation (2002) report the thermogravimetric weight loss from a commercial cresyl diphenyl phosphate as five per cent at 217°C, ten per cent at 236°C and 50 per cent at 285°C. The data refer to a 10 mg sample heated at a rate of 10°C per minute under a nitrogen atmosphere.

These data do not allow emission factors for the service life to be estimated. Factors from the ESD on plastics additives are used, as applied in the risk assessment of medium-chain chlorinated paraffins as appropriate (ECB 2005). These are applied to articles from PVC, adhesives, thermoplastics, thermosets and polyurethane, and to textiles. Volatile losses from products occur at ambient temperatures, and at these temperatures cresyl diphenyl phosphate is considered to have a similar vapour pressure to DEHP, the reference compound. The appropriate factor from the ESD is therefore that for medium volatility substances or 0.05 per cent over the lifetime of the product. An exception to this is where the use is in thin films, where a higher value of 1.9 per cent over the lifetime was used.

Waste in the environment

This considers the loss of substance in particles of plastic material from articles in use. The approach is the same as that used in the risk assessment for medium-chain chlorinated paraffins. For PVC, a loss of 0-3.125 per cent is assumed, depending on the use of the products. For textiles and adhesives, a loss of two per cent of the material over the lifetime of the products or articles is assumed. For other uses

(thermoplastics and polyurethane), no waste generation during the lifetime is assumed. Losses may also occur on disposal at the end of the service life. A figure of two per cent loss on disposal is assumed for all plastic materials. In the calculations, the substance in these particles is assumed to be available in the environment; this is likely to be an overestimate, but there are no actual data to indicate how much may be available. An overall figure of five per cent is used for losses from pigment dispersions to cover the service life and disposal.

3.2.5 Other sources of release

A small quantity of cresyl diphenyl phosphate is not allocated to one of the three use areas. It was assumed that this amount is in fact used in these areas, but passes through a longer supply chain and hence its use is not known to the major producers and suppliers who provided the information. To deal with this, an overall emission factor was derived from the estimated releases from the quantity allocated to specific uses. This factor was applied to the unallocated tonnage, and the release divided between the different compartments in the same ratio as for the allocated tonnage. These releases appear in the summary table (Table 3.4) under miscellaneous uses.

3.2.6 Summary of environmental releases

Estimated environmental releases of cresyl diphenyl phosphate are given in Table 3.4.

Table 3.4 Summary of estimated environmental release of cresyl diphenyl phosphate

Life cycle stage		Local (kg/day)			Regional (kg/year)			Continental (kg/year)		
		Air	Water	Soil	Air	Water[a]	Soil	Air	Water[a]	Soil
Production			1.9 and <2			180 to surface water[b]			<323 to surface water[b]	
Textile coating	Raw materials handling and compounding		0.02							
	Application of coating	0.05	0.05							
	Raw materials handling, compounding and application	0.05	0.07		c	c		c	c	
	In service losses				1.25	12.5		11.25	112.5	
	Waste in the environment[d]				0.09	22.6 to surface water	68	0.82	203 to surface water	613
Thermosets and epoxy resins	Raw materials handling and compounding	0.025	0.075							
	Conversion	0.025	0.025							
	Raw materials handling, compounding and conversion	0.05	0.1		c	c		c	c	
	In service losses				7.05	70.5		63.5	635	
	Waste in the environment[d]				0.28	69.8 to surface water	210	2.5	628 to surface water	1,893

Table 3.4 continued.

Life cycle stage		Local (kg/day)			Regional (kg/year)			Continental (kg/year)		
		Air	**Water**	**Soil**	**Air**	**Water[a]**	**Soil**	**Air**	**Water[a]**	**Soil**
Lubricant additive	Blending	1.7×10^{-9}	1.09×10^{-3}		1.02×10^{-7}	0.0651				
	In service losses[d]					55 to surface water	54		497 to surface water	490
PVC – 1	Raw materials handling and compounding		0.05							
	Conversion	0.125	0.125							
	Raw materials handling, compounding and conversion	0.125	0.175		c	c		c	c	
	In service losses				7.5	75		67.5	675	
	Waste in the environment[d]				0.76	189 to surface water	568	6.8	1,698 to surface water	5,113
PVC – 2	Raw materials handling and compounding	0.0125	0.0375							
	Conversion	0.0625	0.0625							
	Raw materials handling, compounding and conversion	0.075	0.10		c	c		c	c	
	In service losses				2.7	27		24.3	243	
	Waste in the environment[d]				0.11	26.7 to surface water	80.5	0.97	241 to surface water	725

Table 3.4 continued.

Life cycle stage		Local (kg/day)			Regional (kg/year)			Continental (kg/year)		
		Air	**Water**	**Soil**	**Air**	**Water[a]**	**Soil**	**Air**	**Water[a]**	**Soil**
PVC – 3	Raw materials handling and compounding	0.04	0.12							
	Conversion	0.20	0.20							
	Raw materials handling, compounding and conversion	0.24	0.32		c	c		c	c	
	In service losses				955	250		8,595	2,225	
	Waste in the environment[d]				0.98	243 to surface water	731	8.8	2,185 to surface water	6,583
PVC – 4	Raw materials handling and compounding	0.0125	0.0375							
	Conversion	0.0125	0.0125							
	Raw materials handling, compounding and conversion	0.025	0.050		c	c		c	c	
	In service losses				7.25			65.25		
	Waste in the environment[d]				0.058	14.4 to surface water	43.5	0.52	130 to surface water	392
PVC – 5	Raw materials handling and compounding	0.0125	0.0375							
	Conversion	0.0125	0.0125							
	Raw materials handling, compounding and conversion	0.025	0.05		c	c		c	c	
	In service losses				7	1,960		63	17,640	
	Waste in the environment[d]				0.52	128 to surface water	386	4.64	1,154 to surface water	3,476

Table 3.4 continued.

Life cycle stage		Local (kg/day)			Regional (kg/year)			Continental (kg/year)		
		Air	**Water**	**Soil**	**Air**	**Water[a]**	**Soil**	**Air**	**Water[a]**	**Soil**
PVC – 6	Raw materials handling and compounding	0.0125	0.0375							
	Conversion	0.0625	0.0625							
	Raw materials handling, compounding and conversion	0.075	0.10		c	c		c	c	
	In service losses				1.6	448		14.4	4032	
	Waste in the environment[d]				0.2	52.7 to surface water	159	1.9	475 to surface water	1,429
Adhesives	In service losses				2	1,460 to surface water		18	13,140 to surface water	
	Waste in the environment[d]				0.13	32.2 to surface water	96.9	1.16	289	872
Poly-urethane	Raw materials handling and compounding	0.09	0.27							
	Conversion	0.09	0.09							
	Raw materials handling, compounding and conversion	0.18	0.35		c	c		c	c	
	In service losses				54.6			491.4		
	Waste in the environment[d]				2.2	543 to surface water	1,635	19.6	4,886 to surface water	14,717

Table 3.4 continued.

Life cycle stage		Local (kg/day)			Regional (kg/year)			Continental (kg/year)		
		Air	**Water**	**Soil**	**Air**	**Water[a]**	**Soil**	**Air**	**Water[a]**	**Soil**
Thermo-plastic and stryrenics	Raw materials handling and compounding	0.01	0.03							
	Conversion	0.01	0.01							
	Raw materials handling, compounding and conversion	0.02	0.04		c	c		c	c	
	In service losses				4.8×10^{-3}			0.04		
	Waste in the environment[d]				4.0×10^{-3}	1.0 to surface water	3.0	0.036	8.96 to surface water	27
Miscellan-eous					244	651 plus 636 to surface water	905	2,196	5,858 plus 5,725 to surface water	8,145
Total					1,493	7,464	4,928	11,826	63,328	44,530

Notes: a) Regional and continental emissions to water are split 80:20 between waste water treatment and direct discharge to surface water expect where noted.
b) Emissions calculated from site-specific data, after waste water treatment (sludges from production sites are incinerated, calculating the values after treatment allows this to be reflected in the emission estimates).
c) Values for individual steps are confidential, but are included in the total figure.
d) Releases from lubricant use and as waste in the environment are assumed to go directly to surface water.

3.3 Environmental concentrations

3.3.1 Aquatic environment (surface water, sediment and wastewater treatment plant)

Calculation of PECs

PECs for surface water and sediment were estimated with the EUSES 2.0.3[6] program using the data summarised in the previous sections as input. The concentrations predicted for water and sediment are shown in Table 3.5.

The predicted regional concentrations are 0.11 μg/l for surface water and 3.11×10^{-3} mg/kg wet weight for sediment.

Table 3.5 Summary of predicted local concentrations for the aquatic compartment

Scenario		PEC_{local}			
		Microorganisms in sewage treatment plant (mg/l)	**Surface water - emission episode (μg/l)**	**Surface water - annual average (μg/l)**	**Sediment (mg/kg wet wt.)**
Production of cresyl diphenyl phosphate		0.01 and 1.0	0.41 and 0.13	0.40 and 0.12	0.02 and 6.72×10^{-3}
Textile coating	Compounding	2.7×10^{-3}	0.38	0.12	0.02
	Application of coating	6.75×10^{-3}	0.78	0.14	0.04
	Combined compounding and application	9.46×10^{-3}	1.05	0.15	0.06
Thermo-sets and epoxy resins	Compounding	0.01	1.12	0.42	0.06
	Conversion	3.38×10^{-3}	0.45	0.21	0.02
	Combined compounding and conversion	0.01	1.45	0.52	0.08
Adhesives		negligible	negligible	negligible	negligible
Lubricant additive	Blending of lubricant	1.47×10^{-4}	0.12	0.11	6.53×10^{-3}
PVC – 1	Compounding	6.75×10^{-3}	0.78	0.66	0.04
	Conversion	0.02	1.79	1.49	0.09
	Combined compounding and conversion	0.02	2.46	2.04	0.13

[6] The version used was the pre-release final version.

Table 3.5 continued.

Scenario		PEC_{local}			
		Microorganisms in sewage treatment plant (mg/l)	**Surface water - emission episode (μg/l)**	**Surface water - annual average (μg/l)**	**Sediment (mg/kg wet wt.)**
PVC – 2	Compounding	5.07×10^{-3}	0.61	0.52	0.03
	Conversion	8.44×10^{-3}	0.95	0.80	0.05
	Combined compounding and conversion	0.01	1.45	1.22	0.08
PVC – 3	Compounding	0.02	1.72	1.44	0.09
	Conversion	0.03	2.80	2.32	0.15
	Combined compounding and conversion	0.04	4.42	3.65	0.23
PVC – 4	Compounding	5.07×10^{-3}	0.61	0.13	0.03
	Conversion	1.69×10^{-3}	0.28	0.11	0.01
	Combined compounding and conversion	6.75×10^{-3}	0.78	0.13	0.04
PVC – 5	Compounding	5.07×10^{-3}	0.61	0.11	0.03
	Conversion	1.69×10^{-3}	0.28	0.28	0.01
	Combined compounding and conversion	6.75×10^{-3}	0.78	0.66	0.04
PVC – 6	Compounding	5.07×10^{-3}	0.61	0.11	0.03
	Conversion	8.44×10^{-3}	0.95	0.95	0.05
	Combined compounding and conversion	0.01	1.45	1.22	0.08
Thermo-plastics and styrenics	Compounding	4.05×10^{-3}	0.51	0.11	0.03
	Conversion	1.35×10^{-3}	0.24	0.24	0.01
	Combined compounding and conversion	5.4×10^{-3}	0.65	0.55	0.03
Poly-urethane	Compounding	0.04	3.74	3.1	0.20
	Conversion	0.01	1.32	1.1	0.07
	Combined compounding and conversion	0.05	4.82	3.98	0.26

Predicted concentrations were also calculated for the marine environment, using the EUSES program. These are included in Table 3.6. Note that production is not included in this table; the production sites do not discharge to the marine environment.

Table 3.6 Summary of predicted local concentrations for the marine compartment

Scenario		PEC_{local}		
		Marine water - emission episode (μg/l)	**Marine water - annual average (μg/l)**	**Marine sediment (mg/kg wet wt.)**
Textile coating	Compounding	0.11	0.01	5.8×10^{-3}
	Application of coating	0.26	0.02	0.01
	Combined compounding and application	0.36	0.03	0.02
Thermo-sets and epoxy resins	Compounding	0.38	0.13	0.02
	Conversion	0.14	0.05	7.12×10^{-3}
	Combined compounding and conversion	0.51	0.16	0.03
Adhesives		negligible	negligible	negligible
Lubricant additive	Blending of lubricant	0.02	0.01	8.17×10^{-4}
PVC – 1	Compounding	0.26	0.22	0.01
	Conversion	0.63	0.52	0.03
	Combined compounding and conversion	0.88	0.73	0.05
PVC – 2	Compounding	0.20	0.16	0.01
	Conversion	0.32	0.27	0.02
	Combined compounding and conversion	0.51	0.42	0.03
PVC – 3	Compounding	0.61	0.5	0.03
	Conversion	1.01	0.83	0.05
	Combined compounding and conversion	1.6	1.32	0.08
PVC – 4	Compounding	0.2	0.02	0.01
	Conversion	0.07	0.01	3.82×10^{-3}
	Combined compounding and conversion	0.26	0.02	0.01
PVC – 5	Compounding	0.2	0.01	0.01
	Conversion	0.07	0.07	3.82×10^{-3}
	Combined compounding and conversion	0.26	0.22	0.01
PVC – 6	Compounding	0.2	0.01	0.01
	Conversion	0.32	0.32	0.02
	Combined compounding and conversion	0.51	0.42	0.03

Table 3.6 continued.

Scenario		PEC_{local}		
		Marine water - emission episode (μg/l)	**Marine water - annual average (μg/l)**	**Marine sediment (mg/kg wet wt.)**
Thermo-plastics and styrenics	Compounding	0.16	0.01	8.44×10^{-3}
	Conversion	0.06	0.06	3.17×10^{-3}
	Combined compounding and conversion	0.21	0.17	0.01
Poly-urethane	Compounding	1.36	1.12	0.07
	Conversion	0.46	0.38	0.02
	Combined compounding and conversion	1.75	1.44	0.09

Measured levels in water and sediment

Cresyl diphenyl phosphate was monitored in England and Wales over the period November 2007 – April 2008 as part of the Environment Agency's Targeted Risk Based Monitoring (TRBM) initiative. Six samples were collected at approximately weekly intervals from 15 paired WWTP effluent/receiving water sites across all eight Environment Agency Regions. The site selection criteria are not specified – it is likely that most are reasonably large WWTP with mixed industrial/household influent.

The limit of detection was 0.05 µg/l. The substance was only detected once, in the Manchester Ship Canal, at a concentration of 0.053 µg/l. This receives effluent from the Davyhulme WWTP, which serves an industrial complex which includes a production site. However, there could be other sources locally as well, and since the substance was not detected in the WWTP effluent it would seem that sources upstream of the WWTP were involved. This has not yet been investigated further.

Boethling and Cooper (1985) reported that cresyl diphenyl phosphate was not detected (detection limit 10 μg/l) in water samples collected near to an aryl phosphate production site and a large user of hydraulic fluids in the United States.

A survey of the levels of cresyl diphenyl phosphate in surface waters from all over Japan was carried out by Environment Agency Japan (1996). The substance was not detected in 63 samples analysed in 1981 (detection limit in the range 0.05 µg/l).

Hoke *et al.* (1993) determined the levels of cresyl diphenyl phosphate in sediment from the Grand Calumet River, Indiana (industrialised area). In all, ten composite sediment samples were collected during 1988-1990 and cresyl diphenyl phosphate was not detected (detection limit 0.01 mg/kg dry weight) in any of the samples.

A survey of the levels of cresyl diphenyl phosphate in sediments from all over Japan was carried out by Environment Agency Japan (1996). The substance was not detected in 63 samples analysed in 1981 (detection limit in the range 5 µg/kg dry weight).

Comparison of measured levels with predicted levels

The available monitoring data indicate that levels of cresyl diphenyl phosphate in surface water and sediment appear to be low (the substance was generally not detected). However, it is not possible to compare these data directly with levels

predicted close to sources of release for all scenarios considered. Therefore, the predicted concentrations are used in the risk characterisation.

3.3.2 Terrestrial compartment

Calculation of PECs

PECs for the soil compartment were estimated using EUSES 2.0.3 and are summarised in Table 3.7.

Table 3.7 Summary of predicted local concentrations for the air and terrestrial compartments

Scenario		PEC_{local}			
		Annual average conc. in air (mg/m^3)	Agricultural soil – 30 day average (mg/kg wet wt.)	Agricultural soil – 180 day average (mg/kg wet wt.)	Ground-water under agricultural soil (μg/l)
Production of cresyl diphenyl phosphate		6.86×10^{-8} and 4.26×10^{-8}	negligible[a]	negligible[a]	negligible[a]
Textile coating	Compounding	4.26×10^{-8}	6.58×10^{-3}	4.0×10^{-3}	0.09
	Application of coating	6.52×10^{-7}	0.02	9.94×10^{-3}	0.23
	Combined compounding and application of coating	6.52×10^{-7}	0.02	0.01	0.33
Thermo-sets and epoxy resins	Compounding	2.18×10^{-6}	0.02	0.01	0.35
	Conversion	2.18×10^{-6}	8.24×10^{-3}	5.0×10^{-3}	0.12
	Combined compounding and conversion	4.31×10^{-6}	0.03	0.02	0.47
Adhesives		negligible	negligible	negligible	negligible
Lubricant additive	Blending of lubricant	4.26×10^{-8}	3.96×10^{-4}	2.55×10^{-4}	6.0×10^{-3}
PVC – 1	Combined compounding and conversion	2.88×10^{-5}	0.06	0.03	0.82
	Compounding	4.32×10^{-8}	0.02	9.93×10^{-3}	0.23
	Conversion	2.86×10^{-5}	0.04	0.03	0.59
PVC – 2	Combined compounding and conversion	1.72×10^{-5}	0.03	0.02	0.47
	Compounding	2.9×10^{-6}	0.01	7.48×10^{-3}	0.18
	Conversion	1.43×10^{-5}	0.02	0.01	0.30
PVC – 3	Combined compounding and conversion	5.49×10^{-5}	0.11	0.06	1.5
	Compounding	9.18×10^{-6}	0.04	0.02	0.56
	Conversion	4.57×10^{-5}	0.07	0.04	0.94

Table 3.7 continued.

Scenario		PEC_{local}			
		Annual average conc. in air (mg/m^3)	Agricultural soil – 30 day average (mg/kg wet wt.)	Agricultural soil – 180 day average (mg/kg wet wt.)	Ground-water under agricultural soil (μg/l)
PVC – 4	Combined compounding and conversion	2.71×10^{-7}	0.02	9.94×10^{-3}	0.23
	Compounding	1.57×10^{-7}	0.01	7.46×10^{-3}	0.18
	Conversion	1.57×10^{-7}	4.13×10^{-3}	2.51×10^{-3}	0.06
PVC – 5	Combined compounding and conversion	5.75×10^{-6}	0.02	9.98×10^{-3}	0.24
	Compounding	5.21×10^{-8}	0.01	7.46×10^{-3}	0.18
	Conversion	3.52×10^{-6}	4.16×10^{-3}	2.54×10^{-3}	0.06
PVC – 6	Combined compounding and conversion	1.72×10^{-5}	0.03	0.02	0.47
	Compounding	5.21×10^{-8}	0.01	7.46×10^{-3}	0.18
	Conversion	1.74×10^{-5}	0.02	0.01	0.30
Thermo-plastics and styrenics	Combined compounding and conversion	4.61×10^{-6}	0.01	7.99×10^{-3}	0.19
	Compounding	5.02×10^{-8}	9.86×10^{-3}	5.98×10^{-3}	0.14
	Conversion	2.82×10^{-6}	3.34×10^{-3}	2.04×10^{-3}	0.05
Poly-urethane	Combined compounding and conversion	4.12×10^{-5}	0.12	0.07	1.64
	Compounding	2.06×10^{-5}	0.09	0.05	1.26
	Conversion	2.06×10^{-5}	0.03	0.02	0.43

Notes: a) Sewage sludge from the production site is not applied to soil.

The estimated regional concentrations for the soil compartment are summarised below.

$PEC_{regional}$ = 3.44×10^{-5} mg/kg wet weight for agricultural soil
= 8.11×10^{-4} μg/l for pore water of agricultural soil
= 3.91×10^{-5} mg/kg wet weight for natural soil
= 5.01×10^{-3} mg/kg wet weight for industrial soil

Boethling and Cooper (1985) reported that cresyl diphenyl phosphate was not detected (detection limit 0.1 mg/kg) in soil samples collected near to an aryl phosphate production site and a large user of hydraulic fluids in the United States.

It is not possible to compare measured and predicted levels as only a limited number of data are available on measured levels in soil. Predicted concentrations are used in the risk characterisation.

3.3.3 Air compartment

Concentrations of cresyl diphenyl phosphate in air were estimated using EUSES 2.0.3. The PECs calculated are summarised in Table 3.7.

The predicted regional concentration is 4.26×10^{-8} mg/m^3.

Boethling and Cooper (1985) reported that cresyl diphenyl phosphate was not detected (detection limit 2 μg/m^3) in air samples collected near to an aryl phosphate production site and a large user of hydraulic fluids in the United States.

It is not possible to compare measured and predicted levels as only a limited number of data are available on measured levels in air. Predicted concentrations are used in the risk characterisation.

3.3.4 Non-compartment specific exposure relevant for the food chain

Predicted concentrations in biota and food

Predicted concentrations of cresyl diphenyl phosphate in fish and earthworms are shown in Table 3.8 and predicted concentrations in prey species for marine food chains are also included.

Table 3.8 Summary of predicted local concentrations for secondary poisoning

Scenario		Predicted concentration			
		Fish (mg/kg)	**Earthworms (mg/kg)**	**Marine fish (mg/kg)**	**Marine top predators (mg/kg)**
Production of cresyl diphenyl phosphate		0.05 and 0.02	3.07×10^{-4}[a]	n/a	n/a
Textile coating	Application of coating	0.02	0.02	2.44×10^{-3}	2.09×10^{-3}
	Compounding	0.02	0.04	3.09×10^{-3}	2.22×10^{-3}
	Combined compounding and application of coating	0.03	0.06	3.53×10^{-3}	2.31×10^{-3}
Thermo-sets and epoxy resins	Compounding	0.05	0.06	0.01	4.29×10^{-3}
	Conversion	0.03	0.02	5.82×10^{-3}	2.77×10^{-3}
	Combined compounding and conversion	0.06	0.08	0.02	5.06×10^{-3}
Adhesives		negligible	negligible	negligible	negligible
Lubri-cant additive	Blending of lubricant	0.02	1.21×10^{-3}	2.09×10^{-3}	2.02×10^{-3}
PVC – 1	Compounding	0.08	0.04	0.02	6.1×10^{-3}
	Conversion	0.16	0.10	0.05	0.01
	Combined compounding and conversion	0.22	0.15	0.07	0.02
PVC – 2	Compounding	0.06	0.03	0.02	5.07×10^{-3}
	Conversion	0.09	0.05	0.03	7.12×10^{-3}
	Combined compounding and conversion	0.13	0.08	0.04	0.01

Table 3.8 continued.

Scenario		Predicted concentration			
		Fish (mg/kg)	Earthworms (mg/kg)	Marine fish (mg/kg)	Marine top predators (mg/kg)
PVC – 3	Compounding	0.16	0.10	0.05	0.01
	Conversion	0.24	0.17	0.08	0.02
	Combined compounding and conversion	0.38	0.27	0.13	0.03
PVC – 4	Compounding	0.02	0.03	2.62×10^{-3}	2.12×10^{-3}
	Conversion	0.02	0.01	2.21×10^{-3}	2.04×10^{-3}
	Combined compounding and conversion	0.02	0.04	2.82×10^{-3}	2.16×10^{-3}
PVC – 5	Compounding	0.02	0.03	2.05×10^{-3}	2.01×10^{-3}
	Conversion	0.04	0.01	8.23×10^{-3}	3.25×10^{-3}
	Combined compounding and conversion	0.08	0.04	0.02	6.1×10^{-3}
PVC – 6	Compounding	0.02	0.03	2.05×10^{-3}	2.01×10^{-3}
	Conversion	0.11	0.05	0.03	8.23×10^{-3}
	Combined compounding and conversion	0.13	0.08	0.04	0.01
Thermo plastics and styrenics	Compounding	0.02	0.03	2.04×10^{-3}	2.01×10^{-3}
	Conversion	0.04	8.66×10^{-3}	6.98×10^{-3}	3.0×10^{-3}
	Combined compounding and conversion	0.07	0.03	0.02	5.28×10^{-3}
Polyurethane	Compounding	0.32	0.22	0.11	0.02
	Conversion	0.12	0.08	0.04	9.37×10^{-3}
	Combined compounding and conversion	0.41	0.29	0.15	0.03

Predicted concentrations in food for human consumption are shown in Table 3.9. The concentrations have mostly been calculated using EUSES 2.0.

Lombardo and Egry (1979) found cresyl diphenyl phosphate at a concentration of 130 to 410 μg/kg in fish from an area downstream of several metal processing plants in the United States.

The available monitoring data indicate that cresyl diphenyl phosphate may be present in fish near to sources of release. As the monitoring data are limited in scope, the predicted concentrations are used in the risk characterisation.

Table 3.9 Summary of predicted concentrations in food for human consumption

Scenario		Concentration							
		Fish (mg/kg)	Root crops (mg/kg)	Leaf crops (mg/kg)	Drinking water (mg/l)	Meat (mg/kg)	Milk (mg/kg)	Air (mg/m^3)	Total daily human intake (mg/kg bw/day
Production of cresyl diphenyl phosphate		0.08 and 0.02	2.55×10^{-4}	2.11×10^{-4} and 1.31×10^{-4}	2.0×10^{-4} and 6.19×10^{-5}	2.06×10^{-5} and 1.0×10^{-5}	6.51×10^{-6} and 3.16×10^{-6}	2.6×10^{-8}	1.43×10^{-4} and 4.62×10^{-5}
Textile/fabric coating	Compounding	0.02	0.03	1.96×10^{-4}	9.42×10^{-5}	1.35×10^{-5}	4.26×10^{-6}	1.26×10^{-11}	1.88×10^{-4}
	Application of coating	0.03	0.06	2.16×10^{-3}	2.34×10^{-4}	1.26×10^{-4}	3.97×10^{-5}	6.09×10^{-7}	4.45×10^{-4}
	Combined compounding and application of coating	0.03	0.09	2.23×10^{-3}	3.28×10^{-4}	1.32×10^{-4}	4.17×10^{-5}	6.09×10^{-7}	5.94×10^{-4}
Thermo-plastics and styrenics	Compounding	0.02	0.04	2.52×10^{-4}	1.41×10^{-4}	1.78×10^{-5}	5.64×10^{-6}	7.62×10^{-9}	2.58×10^{-4}
	Conversion	0.05	0.01	8.69×10^{-3}	1.22×10^{-4}	4.83×10^{-3}	1.53×10^{-4}	2.78×10^{-6}	3.09×10^{-4}
	Combined compounding and conversion	0.11	0.05	0.01	2.76×10^{-4}	7.95×10^{-4}	2.51×10^{-4}	4.57×10^{-6}	7.26×10^{-4}
Adhesives		negligible	negligible	negligible	negligible	negligible	negligible	negligible	negligible
Lubricant additive	Blending of lubricant	0.02	1.66×10^{-3}	1.35×10^{-4}	5.56×10^{-5}	9.83×10^{-6}	3.11×10^{-6}	2.66×10^{-12}	4.96×10^{-5}
PVC – 1	Compounding	0.13	0.06	2.95×10^{-4}	3.31×10^{-4}	2.72×10^{-5}	8.59×10^{-6}	5.9×10^{-10}	5.87×10^{-4}
	Conversion	0.30	0.16	0.09	7.64×10^{-4}	4.87×10^{-3}	1.54×10^{-3}	2.86×10^{-5}	2.96×10^{-3}
	Combined compounding and conversion	0.41	0.23	0.09	1.02×10^{-3}	4.89×10^{-3}	1.55×10^{-3}	2.86×10^{-5}	3.5×10^{-3}
PVC – 2	Compounding	0.11	0.05	9.02×10^{-3}	2.62×10^{-4}	5.05×10^{-4}	1.6×10^{-4}	2.86×10^{-6}	6.05×10^{-4}
	Conversion	0.16	0.08	0.04	4.0×10^{-4}	2.44×10^{-3}	7.72×10^{-4}	1.43×10^{-5}	1.5×10^{-3}
	Combined compounding and conversion	0.24	0.13	0.05	6.08×10^{-4}	2.94×10^{-3}	9.28×10^{-4}	1.71×10^{-5}	2.06×10^{-3}

Table 3.9 continued.

Scenario		Concentration							
		Fish (mg/kg)	Root crops (mg/kg)	Leaf crops (mg/kg)	Drinking water (mg/l)	Meat (mg/kg)	Milk (mg/kg)	Air (mg/m^3)	Total daily human intake (mg/kg bw/day
PVC – 3	Compounding	0.29	0.16	0.03	7.18×10^{-4}	1.59×10^{-3}	5.04×10^{-4}	9.14×10^{-6}	1.85×10^{-3}
	Conversion	0.46	0.26	0.14	1.16×10^{-3}	7.79×10^{-3}	2.46×10^{-3}	4.57×10^{-5}	4.71×10^{-3}
	Combined compounding and conversion	0.73	0.42	0.17	1.82×10^{-3}	9.37×10^{-3}	2.96×10^{-3}	5.48×10^{-5}	6.51×10^{-3}
PVC – 4	Compounding	0.03	0.05	6.03×10^{-4}	1.76×10^{-4}	3.82×10^{-5}	1.21×10^{-5}	1.14×10^{-7}	3.23×10^{-4}
	Conversion	0.02	0.02	5.22×10^{-4}	5.92×10^{-5}	3.04×10^{-5}	9.62×10^{-6}	1.14×10^{-7}	1.38×10^{-4}
	Combined compounding and conversion	0.03	0.06	9.94×10^{-4}	2.34×10^{-4}	6.13×10^{-5}	1.94×10^{-5}	2.28×10^{-7}	4.22×10^{-4}
PVC – 5	Compounding	0.02	0.05	2.82×10^{-4}	1.76×10^{-4}	2.05×10^{-5}	6.48×10^{-6}	9.52×10^{-9}	3.12×10^{-4}
	Conversion	0.06	0.02	0.01	1.39×10^{-4}	6.01×10^{-4}	1.9×10^{-4}	3.47×10^{-6}	3.77×10^{-4}
	Combined compounding and conversion	0.13	0.06	0.02	3.31×10^{4}	9.91×10^{-4}	3.13×10^{-4}	5.71×10^{-6}	8.97×10^{-4}
PVC – 6	Compounding	0.02	0.05	2.82×10^{-4}	1.76×10^{-4}	2.05×10^{-5}	6.48×10^{-6}	9.52×10^{-9}	3.12×10^{-4}
	Conversion	0.19	0.08	0.05	4.75×10^{-4}	2.97×10^{-3}	9.38×10^{-4}	1.74×10^{-5}	1.72×10^{-3}
	Combined compounding and conversion	0.24	0.13	0.05	6.08×10^{-4}	2.94×10^{-3}	9.28×10^{-4}	1.71×10^{-5}	2.06×10^{-3}
Thermosets and epoxy resins	Compounding	0.08	0.10	6.92×10^{-3}	3.51×10^{-4}	3.9×10^{-4}	1.23×10^{-4}	2.13×10^{-6}	8.01×10^{-4}
	Conversion	0.04	0.03	6.76×10^{-3}	1.18×10^{-4}	3.75×10^{-4}	1.19×10^{-4}	2.13×10^{-6}	3.71×10^{-4}
	Combined compounding and conversion	0.10	0.13	0.01	4.68×10^{-4}	7.58×10^{-4}	2.4×10^{-4}	4.27×10^{-6}	1.13×10^{-3}

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Table 3.9 continued.

Scenario		Concentration							
		Fish (mg/kg)	**Root crops (mg/kg)**	**Leaf crops (mg/kg)**	**Drinking water (mg/l)**	**Meat (mg/kg)**	**Milk (mg/kg)**	**Air (mg/m^3)**	**Total daily human intake (mg/kg bw/day**
Adhesives		negligible	negligible	negligible	negligible	negligible	negligible	negligible	negligible
Polyurethane	Compounding	0.62	0.35	0.06	1.55×10^{-3}	3.57×10^{-3}	1.13×10^{-3}	2.06×10^{-5}	4.1×10^{-3}
	Conversion	0.22	0.12	0.06	5.52×10^{-4}	3.51×10^{-3}	1.11×10^{-3}	2.06×10^{-5}	2.14×10^{-3}
	Combined compounding and conversion	0.80	0.45	0.13	1.99×10^{-3}	7.07×10^{-3}	2.24×10^{-3}	4.11×10^{-5}	6.1×10^{-3}
Regional sources		0.02	2.24×10^{-4}	1.31×10^{-4}	5.44×10^{-5}	9.66×10^{-6}	3.05×10^{-6}	4.26×10^{-8}	4.08×10^{-5}

4 Effects assessment: Hazard identification and dose (concentration) – response (effect) assessment

4.1 Aquatic compartment

The following sections review the available toxicity data for cresyl diphenyl phosphate with aquatic organisms. Where possible, a validity marking is given for each study (this appears in the summary tables within each section). The following validity markings have been used:

1 **Valid without restriction.** The test is carried out to internationally recognised protocols (or equivalent protocols) and all or most of the important experimental details are available.

2 **Use with care.** The test is carried out to internationally recognised protocols (or equivalent protocols) but some important experimental details are missing, or the method used, or endpoint studied, in the test means that interpretation of the results is not straightforward.

3 **Not valid.** There is a clear deficiency in the test that means the results cannot be considered valid.

4 **Not assignable.** Insufficient detail is available on the method used to allow a decision to be made on the validity of the study.

In this risk assessment, toxicity data assigned a validity marking of one or two are considered of acceptable quality when deriving the predicted no effect concentration (PNEC).

One important property when considering the aquatic toxicity data is water solubility. The water solubility of cresyl diphenyl phosphate is around 2.6 mg/l. Several studies have been carried out at concentrations greater than this water solubility and, although this itself does not necessarily invalidate the test (for example, co-solvents or solubility aids could have been used to aid dispersion of the substance in the test media), this introduces some uncertainty in the concentration to which the organisms were exposed in the test. In cases where it is clear that undissolved test substance was present in the test media, the tests have been marked as not valid.

4.1.1 Toxicity to fish

Short-term studies

The short-term toxicity of cresyl diphenyl phosphate to freshwater fish is summarised in Table 4.1.

Table 4.1 Short-term toxicity of cresyl diphenyl phosphate to freshwater fish

Species	Test guide-line	Number of animals/ treatment	Age/ size	Co-solvent	Concs. Tested	N or M	Test conditions						End-point	Control response	Effect conc.	Ref.	Val.
							Media	Temp.	Hard.	pH	Static/ flow	D.O.					
Brachydanio rerio						N					Static		Mortality		96h-LC_{50} = 10 mg/l	Bayer 2002, IUCLID 2000	3
Oryzias latipes	OECD 203	10		Methanol	0.29-3.09 mg/l	N					Semi static		Mortality		96h-LC_{50} = 1.3 mg/l	UNEP 2002	2

Notes: N = Nominal concentration.
M = Measured concentration.
Temp. = Temperature.
Hard. = Water hardness as mg $CaCO_3$/l.
D.O. = Dissolved oxygen (given as mg O_2/l or per cent saturation).
Val. = Validity rating (see Section 4.1): 1) Valid without restriction; 2) Use with care; 3) Not valid; 4) Not assignable.

A study carried out according to OECD guideline 203 included in the SIDS dataset (UNEP 2002) gives a 96-hour LC_{50} of 1.3 mg/l. The composition of the substance used in this test is not clear from the SIDS dossier.

Bayer (2002) report a 96-hour LC_{50} of 10 mg/l for a commercial cresyl diphenyl phosphate in an unpublished test with zebra fish (*Brachydanio rerio*). The same test also appears to be reported in IUCLID (2000) as a 96-hour LC_0 of 8.1 mg/l and a 96-hour LC_{100} of 11.5 mg/l. IUCLID (2000) indicates that the results are based on nominal concentrations using direct weight addition of the test substance. As the LC_x values reported are all above the water solubility of the substance, the validity of these data can be questioned.

A fish 96-hour LC_{50} and a 14-day LC_{50} of 2.3 and 3.0 mg/l respectively can be estimated for cresyl diphenyl phosphate from the log K_{ow} value of 4.51 using the USEPA ECOSAR (version 0.99h) software.

Using the methods given in the TGD, a 96-hour LC_{50} of 1.2 mg/l can be estimated using the equation for polar narcosis (recommended for esters) and a log K_{ow} of 4.51.

No data were found for short-term toxicity of cresyl diphenyl phosphate to marine fish.

Long-term studies

No data were located. A long-term no effect concentration of 0.165 mg/l is predicted by the USEPA ECOSAR program (version 0.99h).

4.1.2 Toxicity to aquatic invertebrates

The available data on toxicity to invertebrates are presented in Table 4.2.

Short-term studies

A study according to OECD guideline 202 included in the SIDS data set (UNEP 2002) gives a 24-hour LC_{50} of 3.7 mg/l. The composition of the substance used in this test is not clear from the SIDS dossier.

Using the methods given in the TGD, a 48-hour EC_{50} of 1.6 mg/l can be estimated for *Daphnia magna* using the equation for polar narcosis (recommended for esters) and a log K_{ow} of 4.51. The USEPA ECOSAR program (version 0.99h) predicts a value of 1.4 mg/l for the same endpoint.

Long-term studies

A study according to OECD guideline 202 included in the SIDS dataset (UNEP 2002) gives a 21-day no observed effect concentration (NOEC) for reproduction of 0.12 mg/l. The composition of the substance used in this test is not clear from the SIDS dossier.

Table 4.2 Toxicity of cresyl diphenyl phosphate to freshwater invertebrates

Species	Test guide-line	Number of animals/ treatment	Age/ size	Co-solvent	Concs. Tested	N or M	Test conditions						End-point	Control resp.	Effect conc.	Ref.	Val.
							Media	Temp.	Hard.	pH	Static/ flow	D.O.					
Daphnia magna	OECD 202	Five per replicate, four replicates		DMSO and HCO-40 (9:1)	2.6-27 mg/l plus solvent control	N					Static		Immob.		24h-LC_{50} = 3.7 mg/l	UNEP 2002	2
Daphnia magna	OECD 202	10 per replicate, four replicates		DMSO and HCO-40 (9:1)	0.038-3.8 mg/l plus solvent control	N					Semi static		Repro-duction		NOEC = 0.12 mg/l	UNEP 2002	2

Notes: N = Nominal concentration.
M = Measured concentration.
Temp. = Temperature.
Hard. = Water hardness (given as mg $CaCO_3$/l).
D.O. = Dissolved oxygen (given as mg O_2/l or per cent saturation).
Val. = Validity rating (see Section 4.1): 1) Valid without restriction; 2) Use with care; 3) Not valid; 4) Not assignable.

4.1.3 Toxicity to algae

The toxicity of cresyl diphenyl phosphate to freshwater algae is given in Table 4.3.

A study according to OECD guideline 201 included in the SIDS dataset (UNEP 2002) gives a 72-hour EC_{50} of 0.99 mg/l and a NOEC of 0.55 mg/l. The composition of the substance used in this test is not clear from the SIDS dossier.

Wong and Chau (1984) carried out studies to investigate the toxicity of cresyl diphenyl phosphate (no information on purity) to algae. The experiments investigated the effects on the primary production (as measured by ^{14}C-uptake from ^{14}C-carbonate) in cultures of *Scenedesmus quadricauda* and *Ankistrodesmus falcatus* over a four-hour period. Tests were carried out by inoculating 13.9 ml of growth medium with 1 ml of algal cell culture (7×10^5 cells per ml giving an initial inoculum concentration of 4.7×10^4 cells per ml in the test solution; the algal cells were in the logarithmic growth phase) and incubating for 24 hours with the test substance. The test substance was added as a solution in acetone (final acetone concentration in the test solution was below 0.05 per cent and an acetone control was also run at this concentration). After the initial 24-hour incubation, 0.1 ml of a sodium ^{14}C-carbonate solution was added and the solution was incubated for a further four hours. At the end of four hours, the amount of radioactivity taken up by the cells (corrected for the uptake in dark controls) was determined and the concentration causing a 50 per cent reduction in primary production (IC_{50}) was found to be 0.70 mg/l for *A. falcatus* and 1.0 mg/l for *S. quadricauda*. A similar experiment using natural phytoplankton from Lake Ontario yielded a 4-hour IC_{50} of 0.5 mg/l. These values are taken as 26-hour results, the mid-point of the observation period.

The USEPA ECOSAR program (version 0.99h) predicts a 96-hour EC_{50} value of 0.2 mg/l and a long term no effect concentration of 0.17 mg/l for green algae.

No data were located for the toxicity of cresyl diphenyl phosphate to saltwater algae.

4.1.4 Toxicity to microorganisms

Bayer (2002) and IUCLID (2000) reported an EC_{50} for inhibition of respiration of activated sludge organisms of above 10,000 mg/l for a commercial cresyl diphenyl phosphate product in an unpublished study. The method used conformed to OECD 209 and ISO 8192.

4.1.5 Toxicity to sediment organisms

No data were located.

Table 4.3 Toxicity of cresyl diphenyl phosphate to freshwater algae

Species	Test guide-line	Initial inoculum conc.	Co-solvent	Concs. Tested	N or M	Test conditions				Endpoint	Control response	Effect conc.	Ref.	Val.
						Media	Temp.	Hard.	pH					
Ankistrodesmus falcatus		4.7×10^4 cells/ml	Acetone at ≤0.05%.	Solvent control and dark control run.	N	CHU-10 medium	20°C			Primary production (uptake of ^{14}C)	Uptake in dark control was <5% of total seen in solvent control.	26h-IC_{50} = 0.70 mg/l	Wong and Chau 1984	2
Scenedesmus quadricauda		4.7×10^4 cells/ml	Acetone at ≤0.05%.	Solvent control and dark control run.	N	CHU-10 medium	20°C			Primary production (uptake of ^{14}C)	Uptake in dark control was <5% of total seen in solvent control.	26h-IC_{50} = 1.0 mg/l	Wong and Chau 1984	2
Natural algal community			Acetone at ≤0.05%.	Solvent control and dark control also run.	N	CHU-10 medium	20°C			Primary production (uptake of ^{14}C)	Uptake in dark control was <5% of total seen in solvent control.	26h-IC_{50} = 0.50 mg/l	Wong and Chau 1984	2
Selenastrum capricornutum[7]	OECD 201		Methanol	Solvent control run	N					Biomass		72h-EC_{50} = 0.99 mg/l 72h-NOEC = 0.55 mg/l	UNEP 2002	2

Notes: N = Nominal concentration.
M = Measured concentration.
Temp. = Temperature.
Hard. = Water hardness (given as mg $CaCO_3$/l).
D.O. = Dissolved oxygen (given as mg O_2/l or per cent saturation)
Val. = Validity rating (see Section 4.1): 1) Valid without restriction; 2) Use with care; 3) Not valid; 4) Not assignable

[7] Now *Pseudokirchneriella subcapitata.*

4.1.6 Predicted no effect concentration (PNEC) for the aquatic compartment

Surface water

Acute toxicity levels have been found for cresyl diphenyl phosphate with fish, invertebrates and algae, at 1.3, 3.7 and 0.99 mg/l respectively, although all of these studies are classed as valid with restriction because the identity of the test substance was not provided in detail. The predicted acute L(E)C_{50} for fish and *Daphnia magna* are around 1.2 and 1.6 mg/l respectively. Also, 26-hour IC_{50}s of 0.5-1.0 mg/l have been determined for primary production in non-standard algal studies.

Long-term studies which are valid with restriction are available for invertebrates and algae, with NOEC values of 0.12 and 0.55 mg/l respectively. Annex B considers the available toxicity data for fish for all triaryl phosphates and based on a read-across of these data, the expected long-term toxicity of cresyl diphenyl phosphate to fish is a NOEC of 0.014 mg/l. This value is somewhat lower than predicted values for fish from the ECOSAR program.

Based on the combined dataset including the read-across value, an indicative predicted no effect concentration (PNEC) for the aquatic compartment of 1.4 μg/l can be estimated for cresyl diphenyl phosphate, using an assessment factor of 10 on the predicted NOEC for fish. This value is used as a PNEC in the provisional risk characterisation. There are some uncertainties in this approach, relating to the read-across from other substances and to the composition of the substance tested in many studies. If only the measured results were used, the PNEC would be higher at 2.4 μg/l (based on the lowest NOEC of 0.12 mg/l and an assessment factor of 50).

For the marine environment, an assessment factor of 100 would be used on the lowest NOEC rather than 10, so the PNEC would be 0.14 μg/l.

Microorganisms

An EC_{50} of above 10,000 mg/l was determined for cresyl diphenyl phosphate in an activated sludge respiration inhibition test. According to the TGD, an assessment factor of 100 is appropriate for this type of test result, and so the $PNEC_{microorganisms}$ is estimated to be above 100 mg/l. Although the water solubility of the test substance was exceeded in this test, the actual solubility in pure water may not be relevant to the exposure of microorganisms during waste water treatment.

Sediment

No sediment toxicity data are available for cresyl diphenyl phosphate. In the absence of data, the equilibrium partitioning method can be used to estimate the PNEC.

$$PNEC_{sed} = \frac{K_{susp-water}}{RHO_{susp}} \times PNEC_{water} \times 1000$$

where $K_{susp\text{-}water}$ = suspended sediment-water partition coefficient = 61 m^3/m^3 (see Section 3.1.2).

RHO_{susp} = bulk density of suspended sediment = 1,150 kg/m^3.

Using the indicative PNEC value of 1.4 μg/l derived for water, the provisional $PNEC_{sed}$ can be estimated as 0.074 mg/kg wet weight. This is used in the provisional risk characterisation. The value for marine sediment is 7.4 μg/kg wet weight.

4.2 Terrestrial compartment

None of the terrestrial toxicity data are suitable for determining a PNEC for cresyl diphenyl phosphate. In the absence of data, the equilibrium partitioning method can be used to estimate the PNEC.

$$PNEC_{soil} = \frac{K_{soil-water}}{RHO_{soil}} \times PNEC_{water} \times 1000$$

where $K_{soil-water}$ = soil-water partition coefficient = 72 m^3/m^3 (see Section 3.1.2).

RHO_{soil} = bulk density of wet soil = 1,700 kg/m^3.

Using the indicative PNEC value of 1.4 μg/l derived for water, the provisional $PNEC_{soil}$ can be estimated as 0.059 mg/kg wet weight. This value is used in the provisional risk characterisation.

4.3 Atmosphere

No information is available on the toxicity of cresyl diphenyl phosphate to plants and other organisms exposed via air. The low vapour pressure of the substance means that volatilisation to the atmosphere is likely to be limited and the resulting concentrations are likely to be low. The possibility of cresyl diphenyl phosphate contributing to atmospheric effects such as global warming and acid rain is thus likely to be small. In addition, as the substance does not contain halogen atoms, it will not contribute to ozone depletion.

4.4 Mammalian toxicity

4.4.1 Toxicokinetics, metabolism and distribution

Vainiotalo *et al*. (1987, cited in BG Chemie 2000) administered a single intraperitoneal injection of technical grade cresyl diphenyl phosphate (45 per cent cresyl diphenyl phosphate; Disflamoll DPK/25E) in olive oil at doses of 75, 150 or 300 mg/kg bodyweight, to five rats. The animals were then observed for 14 days (no further study details given). Four hours after administration, the blood concentration of cresyl diphenyl phosphate was 0.3 ± 0.2 μg/g. After 24 hours, the blood concentration had fallen below the limit of detection (0.2 μg/g). The concentrations found in the liver after four and 24 hours were 45.8 ± 28.1 and 1.7 ± 2.5 μg/g tissue, respectively. Overall, it appears that cresyl diphenyl phosphate is rapidly eliminated from the body. In addition, liver activities of cytochrome P450, cytochrome b_5, ethoxycoumarin O-deethylase and ethoxyresorufin O-deethylase were significantly increased within 24 hours of treatment. The activities of these enzymes were reported to return to initial values by seven days post-treatment, although it is not clear at which of the dose levels these changes occurred. Cytochrome c reductase activity was, however, significantly reduced at the highest dose throughout the 14-day post-treatment observation period.

There are no publicly available studies on the metabolism of cresyl diphenyl phosphate. However, it is assumed that, based on the known biotransformation of substances such as tri-*ortho*-cresyl phosphate, the *ortho*-isomer can undergo cyclisation to neurotoxic phenyl saligenin phosphate, whereas this type of metabolism could not occur with the *meta*- and *para*-isomers due to steric hindrance involving the alkyl group as discussed in Section 4.4.6 on neurotoxicity.

4.4.2 Acute toxicity

Only data on experimental animals are available.

Acute lethality studies have been carried out in various species, but these are generally conducted pre-1980 and do not fully conform to current guidelines, such as the OECD guidelines or Good Laboratory Practice (GLP). Table 4.4 (taken from BG Chemie 2000) summarises all of the available acute toxicity data.

Oral

A number of oral studies have been conducted in rats, mice, rabbits, guinea pigs and hens, and are summarised in Table 4.4.

Johannsen *et al*. (1977) conducted a study in Sprague-Dawley rats (male and female, but number not stated). The animals were administered doses of cresyl diphenyl phosphate (purity not reported) in corn oil at up to 15,800 mg/kg bodyweight (individual doses not stated). There was a 14-day post-exposure observation period during which mortality was monitored but detailed mortality data were not reported. The LD_{50} was stated to be 10,400 mg/kg bodyweight. UNEP (2002) and BG Chemie (2000) include a number of other studies but no methodological information or detailed results are given. In addition, important information, such as the purity and isomeric composition of cresyl diphenyl phosphate used, is usually not included. Therefore it is not possible to fully interpret the significance of these data. However, on a weight of evidence basis, it may be concluded that cresyl diphenyl phosphate is of low acute oral toxicity, with LD_{50}s falling within the ranges of above 1,300-19,795 mg/kg bodyweight for rats (both sexes tested and observed for up to 14 days), 6,400-12,800 mg/kg bodyweight for mice (no information as to sex tested or observation period), 893-1,183 mg/kg bodyweight for rabbits (females, observed for 14 days), 1,600-3,200 mg/kg bodyweight for guinea pigs (no information as to sex tested or observation period) and above 5,000-12,000 mg/kg bodyweight for hens (females, observed for up to 42 days).

Inhalation

Two inhalation studies are summarised in UNEP (2002) and BG Chemie (2000). However, reporting detail is limited and the validity of the studies is thus uncertain.

In one study, groups of six male mice (strain not given) were exposed to cresyl diphenyl phosphate vapour (concentrations not given) for six to seven hours. With the exception of mild mucous membrane irritation, no treatment-related signs were observed during exposure or a subsequent 10-14 day observation period (Younger Laboratories 1971, cited in BG Chemie 2000, UNEP 2002).

Table 4.4 Acute toxicity of cresyl diphenyl phosphate

Species	No. of animals/dose	Sex	Route of administration	Observation period (days)	LD_{50} (mg/kg bw, 95% confidence interval)	Reference
Rat (Sprague-Dawley)	5-6	male female	oral	n. d.	18,500 (17,850-19,795)	Younger Laboratories 1958
Rat	5	male female	oral	7	1,420 (1,300-1,550)	Younger Laboratories 1972c
Rat (BOR:WISW)	5	male female	oral	14	>6,000	Bayer 1982
Rat	n. d.	n. d.	oral	n. d.	6,400-1,2800	Sandmeyer and Kirwin 1981
Rat	5	male female	oral	7	6,700 (6,030-7,440)	Younger Laboratories 1973
Rat	5	male female	oral	7	8,250 (7,340-9,280)	Younger Laboratories 1972b
Rat	6	male	oral	14	>40,000	AMR 1974
Rat	5	male female	oral	14	>20,000	FDRL 1976a
Rat	5	male female	oral	14	<20,000 (LD_{90})	FDRL 1976b
Rat	5	male female	oral	7	10,400 (9,260-11,650)	Younger Laboratories 1972a
Rat (Sprague-Dawley	n. d.	male female	oral	14	10,400	Johannsen *et al*. 1977
Rat	n. d.	n. d.	oral	n. d.	>4,000	Mallette and von Haam 1952
Rat	n. d.	male female	oral	n. d.	>4,311	Weeks and Pope 1974
Rat	5	male female	oral	7	>10,000 <12,600	Younger Laboratories 1971
Mouse	n. d.	n. d.	oral	n. d.	6,400-12,800	Sandmeyer and Kirwin 1981
Rabbit	5	female	oral	14	1,028 (893-1,183)	Bayer 1976
Rabbit	1-2	male female	oral	10	1,500-2,500 (minimum lethal dose)	Younger Laboratories 1956

Table 4.4 continued.

Species	No. of animals/dose	Sex	Route of administration	Observation period (days)	LD_{50} (mg/kg bw, 95% confidence interval)	Reference
Guinea pig	n. d.	n. d.	oral	n. d.	1,600-3,200	Sandmeyer and Kirwin 1981
Hen	n. d.	female	oral	14	>10,000	Johannsen *et al*. 1977, Monsanto 1977
Hen	5	n. d.	oral	42	>12,000	Bayer 1976
Hen	2	female	oral	14	>10,000	IBT 1972 a, b
Rabbit	n. d.	n. d.	dermal	n. d.	>5,000	Monsanto 1977
Rabbit	n. d.	male female	dermal (24 hours, occlusive)	14	>5,000	Johannsen *et al*. 1977
Rabbit	10	n. d.	dermal	14	>10,000	FDRL. 1976a
Rabbit	10	male female	dermal	14	>10,000	FDRL 1976b
Rabbit	1-2	male female	dermal	n. d.	Around 5,000 (minimum lethal dose)	Younger Laboratories 1958
Rabbit	1	male female	dermal (24 hours, occlusive)	14	>1,260 <2,000 (minimum lethal dose)	Younger Laboratories 1972b
Rabbit	1	male female	dermal (24 hours, occlusive)	14	>2,000 <3,160 (minimum lethal dose)	Younger Laboratories 1971
Rabbit	1-2	male female	dermal (24 hours, occlusive)	14	>2,000 <3,160 (minimum lethal dose)	Younger Laboratories 1973
Rabbit	1-2	male female	dermal (24 hours occlusive)	14	>5,010 <7,940 (minimum lethal dose)	Younger Laboratories 1972a
Rabbit	1-2	male female	dermal (24 hours occlusive)	14	>7,940 (minimum lethal dose)	Younger Laboratories 1972c
Rat	n. d.	n. d.	intraperitoneal	n. d.	>1,000	Mallette and von Haam 1952
Rat	n. d.	male	intraperitoneal	n. d.	>851	Weeks and Pope 1974
Rat	n. d.	female	intraperitoneal	n. d.	>1,272	Weeks and Pope 1974
Hen	5	n. d.	intraperitoneal	42	>6,000	Bayer 1976

n. d. no data

Source: BG Chemie (2000).

In the second study, two sheep were exposed to an aerosol of undiluted cresyl diphenyl phosphate for one hour at an apparent mean concentration of 0.35 mg/l cresyl diphenyl phosphate. This very high concentration meant that, at times, the sheep were not visible through the aerosol. Transient, minor signs of mucous membrane irritation were the only treatment-related symptoms reported during exposure and a six-week observation period (Bayer 1964, cited in BG Chemie 2000, UNEP 2002).

Dermal

Several dermal studies in the rabbit are available (Table 4.4).

Johannsen *et al*. (1977) applied undiluted cresyl diphenyl phosphate (purity and composition not stated) to the intact dorsal skin of male and female New Zealand white rabbits (number not specified) under occlusive conditions, for 24 hours. At the end of the treatment period, residue material was washed off and the animals were observed for 14 days, after which all animals were subject to necropsy. Details of necropsy findings were not reported. None of the animals died during the study period, so the LD_{50} was above the maximum dose (individual dose levels used not reported) of 5,000 mg/kg bodyweight.

UNEP (2002) and BG Chemie (2000) identify a number of other studies but provide no methodological information or detailed results. In particular, important information such as test substance purity is usually not presented, making it impossible to judge the validity. However, on a weight of evidence basis cresyl diphenyl phosphate may be considered of low acute dermal toxicity, with an LD_{50} of above 1,260-10,000 mg/kg bodyweight.

Other

Vainiotalo *et al*. (1987, cited in BG Chemie 2000) administered a single intraperitoneal injection of technical grade cresyl diphenyl phosphate to groups of five rats (strain and sex not given) at doses of 75, 150 or 300 mg/kg bodyweight; the composition of the test substance was 45 per cent cresyl diphenyl phosphate, 35 per cent triphenyl phosphate, 18 per cent dicresyl phenyl phosphate and two per cent tricresyl phosphate. Relative to the total cresyl content, the percentage of *ortho*-cresyl isomer was reported to be less than 0.09 per cent. The highest dose of 300 mg/kg bodyweight resulted in a significant decrease in pseudocholinesterase activity (reduced to 38 and 26 per cent, at four and 24 hours respectively). A decrease in this parameter was also observed at 150 mg/kg bodyweight, but no further details were given. No such effect was observed at the lowest dose. The activity of brain 2',3'-cyclic nucleotide-3'-phosphohydrolase was also reported to be significantly inhibited throughout the 14-day observation period, but neither the magnitude of the effect or the dose groups affected were reported.

Following treatment, electron microscopy revealed an increase in lipid droplets, proliferation of smooth endoplasmic reticulum and enlarged mitochondria, with an increased number of cristae in the hepatocytes of high-dose group rats; the time of observation of these effects was not clearly reported although it was stated that liver pathology had resolved by the end of the 14-day observation period (BG Chemie 2000).

In a poorly reported study, Mallette and von Haam (1952) noted that cresyl diphenyl phosphate was fatal to rats (strain and sex not given) following intraperitoneal doses higher than one g/kg bodyweight. The rats were described as lethargic by the second or third day after treatment, and went on to develop profuse diarrhoea. Animals died

following symptoms of paralysis. Necropsy findings were generalised capillary paralysis, with severe oedema and numerous haemorrhages in the brain.

Table 4.4 also summarises an additional three studies using intraperitoneal administration which show that the LD_{50}s for cresyl diphenyl phosphate following intraperitoneal administration are high. Therefore, cresyl diphenyl phosphate is considered of low acute toxicity via this route.

Summary of acute toxicity

No information is available from human studies.

No studies conducted to test guidelines are available for acute oral toxicity. However, the many limited studies allow a weight of evidence approach. After oral administration in rats, mice, rabbits, guinea pigs and hens, LD_{50} values are in the range 893 (rabbits) to approximately 20,000 mg/kg bodyweight (rats), falling generally above the current limit dose (2,000 mg/kg bodyweight) applied in modern studies, which shows the compound to be of low toxicity after oral administration.

Transient, minor mucous membrane irritation was the only treatment-related symptom observed following inhalation of cresyl diphenyl phosphate as an aerosol or vapour. Although high concentrations were tested, no information on achieved concentration was given in one study while, in the other, no deaths were observed following exposure to concentrations of 0.35 mg/l for one hour.

The toxicity of cresyl diphenyl phosphate following dermal application is very low, with LD_{50}s above 2,000 mg/kg bodyweight in rabbits.

Several studies using intraperitoneal administration in rats and hens are available. These studies confirm that cresyl diphenyl phosphate is of low acute toxicity, with LD_{50}s in the range of above 851 (male rats) to above 6,000 mg/kg bodyweight (hens).

4.4.3 Irritation

Skin

Two studies on cresyl diphenyl phosphate have been conducted to OECD test guideline 404 ‘Acute dermal irritation/corrosion’ although their GLP status is not known. However, only limited summaries of these studies are available from BG Chemie (2000). UNEP (2002) also reports these studies but does not provide any extra information. Many other skin irritation studies using cresyl diphenyl phosphate were conducted prior to the adoption of OECD test guideline 404 in 1982. Where available, information regarding these studies has been included in Table 4.5 (taken from BG Chemie 2000).

Ciba-Geigy (1984a, cited in BG Chemie 2000, UNEP 2002) investigated the skin irritation potential of cresyl diphenyl phosphate (product tested: Reomol CDP) in a study conducted to OECD test guideline 404. The test material (purity not known) was applied on a four-cm patch to the shaved backs of four California rabbits (sex not given) under occlusive conditions for four hours. Signs of irritation were scored at 30-60 minutes, 48 and 72 hours after removal of the occlusive patch. Slight to well-defined erythema was observed in three animals 30 to 60 minutes after treatment. However, the signs were no longer apparent by 72 hours.

Table 4.5 Irritating effects of diphenyl cresyl phosphate on the dorsal skin of the rabbit

Product	Guideline and/or dose, route, duration*	Findings	Reversibility	Assessment (by the authors)	Reference
Reomol CDP	OECD guideline No. 404	Mild to marked erythema in three animals after 30 to 60 minutes	Reversible within 72 hours	No information	Ciba-Geigy 1984a
Disflamoll DPK	OECD guideline No. 404	No effects after 1, 24, 48, 72 hours and after 8 days (irritation score 0)	-	Not irritating	FhG 1982a
Kronitex 300, SS-578	According to Draize (16 CFR 1500.41), 24-hour application of 0.5 ml to the intact and the scarified skin	At 24 hours, intact skin: erythema 3/6, oedema 0/6; scarified skin: erythema 6/6 (score 1 to 3), oedema 1/6 (score 1); overall average irritation score 0.46	Reversible after 72 hours	Not irritating	FDRL 1976a
Kronitex CDP, SS-578	According to Draize (16 CFR 1500.41), 24-hour application to the intact and the scarified skin	At 24 hours, intact skin: erythema 3/6 (score1), oedema 2/6 (score 1); scarified skin: erythema 3/6 (score 1), oedema 4/6 (score 1); scarified skin after 72 hours: oedema 2/6 (score 1); scarified skin 2/6 (score 1), oedema 0/6; overall average irritation score 0.67	Not fully reversible after 72 hours (not observed for longer periods)	Mildly irritating	FDRL 1976b
Santicizer 140	A 24-hour application of 0.5 ml to the intact and the scarified skin	At 24 and 72 hours and at 7 days, intact skin: no irritation; scarified skin: at 24 hours, very mild erythema around the abrasion site in one animal	Scarified skin: reversible after 72 hours and after 7 days	Intact skin: not irritating, scarified skin: mildly irritating at the most	Weeks and Pope 1974
Santicizer 140	According to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	No irritation within 7 days	-	Not irritating	Younger Laboratories 1973
Santicizer 140	According to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	No irritation within 7 days	-	Not irritating	Younger Laboratories 1972a
Santicizer 140	According to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	No irritation within 7 days	-	Not irritating	Younger Laboratories 1972b

Table 4.5 continued.

Product	Guideline and/or dose, route, duration*	Findings	Reversibility	Assessment (by the authors)	Reference
CP31862-2-AG143546	According to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	No irritation within 7 days	-	Not irritating	Younger Laboratories, 1972c
Cresyl diphenyl phosphate Ciba-Geigy	According to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	At 24 hours mild irritation in 3/3 animals (score 1 of a maximum of 8)	Reversible after 48 hours	Mildly irritating	Younger Laboratories 1971
OS-104	According to Draize, 24-hour occlusive application of 0.5 ml neat substance to the intact skin	No irritation within 72 hours	-	Not irritating	Younger Laboratories 1958
Santicizer 140	No information	Moderately irritating (no further details)	Not investigated	Moderately irritating	Mallette and von Haam 1952

Source: BG Chemie (2000).
Notes: No indications of purity of tested substances. * - where indicated.

FhG (1982a, cited in BG Chemie 2000, UNEP 2002) also conducted a study according to OECD test guideline 404 (product tested: Disflamoll DPK, cresyl diphenyl phosphate purity not known). No signs of irritation were observed 1, 24, 48 and 72 hours or eight days after application of cresyl diphenyl phosphate to rabbit skin; the irritation score was zero. Thus, cresyl diphenyl phosphate does not appear to be a skin irritant.

In the majority of other studies identified, which were conducted before the introduction of OECD test guideline 404, cresyl diphenyl phosphate did not cause skin irritation to intact skin and when using occlusive dressings (see Table 4.5). Two studies showed cresyl diphenyl phosphate (unknown purity) to be mildly irritating to skin, with reversibility in one by 48 hours (Younger Laboratories 1971, cited in BG Chemie 2000) and incomplete reversibility in the other by 72 hours (FDRL 1976b, cited in BG Chemie 2000). Only one study reported cresyl diphenyl phosphate as a moderate skin irritant (Mallette and von Haam 1952). In this patch testing of 15 to 30 subjects, cresyl diphenyl phosphate (as a ten per cent solution of Santicizer 140) was reported to cause slight irritation to the skin of ten per cent of the subjects, but this old study was poorly reported and is of uncertain validity.

Overall, the weight of evidence suggests that cresyl diphenyl phosphate is not irritating or, at worst, slightly irritating to skin.

Human data

Mallette and Haam (1952) tested the potential irritancy of cresyl diphenyl phosphate to human skin by application of cresyl diphenyl phosphate (as Santicizer 140) to the skin of 15 to 30 human volunteers (exact numbers not given). Reactions were classified as slight, moderate or severe. In 90 per cent of the volunteers no reaction was seen, while ten per cent had a slight reaction. Based on this limited study, the degree of skin irritation in humans appears to be similar to that in experimental animals.

Eye

Ciba-Giegy (1984b) and FhG (1982b) conducted studies on cresyl diphenyl phosphate products to OECD test guideline 405 ‘Acute eye irritation/corrosion’ (GLP status not known) but few details are given in the report by BG Chemie (2000). Many other skin irritation studies using cresyl diphenyl phosphate were identified but were conducted prior to the adoption of OECD test guideline 405 in 1981. Information regarding the various studies, as available, is presented in Table 4.6 (taken from BG Chemie 2000).

Ciba-Geigy (1984b, cited in BG Chemie 2000, UNEP 2002) investigated the eye irritation potential of cresyl diphenyl phosphate (product tested: Reomol CDP) in a study conducted to OECD test guideline 405. The test material (purity not known) was administered as a 0.1 ml droplet into one eye of each of four California rabbits (sex not given). The eyelids were then held shut for one second. One, 24 and 72 hours after treatment, eyes were examined for signs of irritation using a direct ophthalmoscope. Very mild conjunctival irritation (no further details given) was reported for three of the rabbits. However, this effect was reversed by 72 hours. The authors concluded that cresyl diphenyl phosphate is mildly irritating to the eye.

FhG (1982b, cited in BG Chemie 2000, UNEP 2002) conducted a study according to OECD test guideline 405 (product tested: Disflamoll DPK, cresyl diphenyl phosphate purity not known). After one hour, some discharge was observed in two of the three rabbits tested but this reversed by 24 hours. The authors of the study concluded that cresyl diphenyl phosphate is not irritating to eyes.

Table 4.6 Irritating effects of diphenyl cresyl phosphate on the mucous membranes of rabbit eye

Product	Guideline and/or dose, route, duration*	Findings	Reversibility	Assessment (by the authors)	Reference
Reomol	OECD guidelines No. 405	Very mild conjunctival irritation in 3/4 animals (no further details)	Reversible after 72 hours	Mildly irritating	Ciba-Geigy 1984b
Disflamoll	OECD guideline No. 405	Discharge in 2/3 animals after one hour, no other effects	Reversible after 24 hours	Not irritating	FhG 1982b
Kronitex 300, SS-578	According to 16 CFR 1500.42, 0.1 ml neat substance for 24 hours, six animals with unwashed eyes, three with eyes washed after four seconds	No effects after 24, 48, 72 hours and after 7 days in the unwashed and the washed eyes	-	Not irritating	FDRL 1976a
Kronitex CDP, SS-578	According to 16 CFR 1500.42, 0.1 ml neat substance for 24 hours, six animals with unwashed eyes, three with eyes washed after four seconds	No effects after 24, 48, 72 hours and after 7 days in the unwashed and the washed eyes	-	Not irritating	FDRL 1976b
Santicizer 140	0.1 ml neat substance for 24 hours	No effects on the cornea, iris and conjunctivae (six rabbits)	-	Not irritating	Weeks and Pope 1974
Santicizer 140)	According to Draize, 0.1 ml neat substance for 24 hours	At 10 minutes and one hour mild to moderate erythema, very mild oedema, discharge, at 24 hours slight erythema, slight discharge; average score 11.3 out of 110	Reversible after 48 hours and after 7 days	Mildly irritating	Younger Laboratories 1973
Santicizer 140	According to Draize, 0.1 ml neat substance for 24 hours	At 10 minutes slight erythema, moderate discharge, at one hour slight erythema, discharge, average irritation score 8/11; at 24 hours discharge, average irritation score 4/110	Reversible after 48 hours	Mildly irritating	Younger Laboratories 1972a
Santicizer 140	According to Draize, 0.1 ml neat substance for 24 hours	At 10 minutes mild to moderate erythema, very mild oedema in 2/3 animals, discharge; at one hour mild to moderate erythema, discharge, average score 9.3 out of 110; at 24 hours slight erythema and discharge	Reversible after 48 hours	Mildly irritating	Younger Laboratories 1972b

Table 4.6 continued.

Product	Guideline and/or dose, route, duration*	Findings	Reversibility	Assessment (by the authors)	Reference
CP 31862-2-AG143546	According to Draize, 0.1 ml neat substance for 24 hours	At 10 minutes mild erythema, very mild oedema, moderate discharge; at one hour moderate erythema, slight oedema and moderate discharge; at 24 hours mild to moderate erythema, moderate discharge	Reversible after 48 hours	Mildly irritating	Younger Laboratories 1972c
Diphenyl cresyl phosphate – Ciba-Geigy UK Limited	According to Draize, 0.1 ml neat substance for 24 hours	At 10 minutes moderate discharge; at one hour slight erythema, moderate discharge, average irritation score 6/110	Reversible after 24 hours	Mildly irritating	Younger Laboratories 1971
OS-104	According to Draize, 0.1 ml neat substance for 24 hours	At one hour moderate reddening of the conjunctivae, mild oedema and discharge, average irritation score at one hour 6.6/110, at 4 hours 8.0/110, at 24 hours 4.6/110, at 48 hours 2.6/110	Reversible after 72 hours	Mildly irritating	Younger Laboratories 1958

Source: BG Chemie (2000).
Notes: No indications of purity of tested substances. * - where indicated.

As can be seen (Table 4.6), the majority of other eye irritation studies were conducted prior to the adoption of OECD test guideline 405. The results of these investigations show cresyl diphenyl phosphate (various products with no information on purity) to be either not irritating or only mildly irritating to the eye, with most signs of irritation reversible within 48 hours of treatment.

Summary of irritation

Cresyl diphenyl phosphate was not irritating to the skin of 90 per cent of human volunteers in a limited study; the remaining ten per cent showed signs of slight irritation. The balance of evidence from several studies in rabbits from which only limited data is available is that cresyl diphenyl phosphate is not irritating to intact skin but is mildly irritating to the eye.

4.4.4 Corrosivity

None of the studies available on skin or eye irritation suggest that cresyl diphenyl phosphate has corrosive properties.

4.4.5 Sensitisation

The paper by Mallette and von Haam (1952) which is considered to be of uncertain validity is the only publicly available source of data on the skin-sensitising potential of cresyl diphenyl phosphate in experimental animals or humans. In this, challenge of 15 to 30 subjects, 14 days after a previous patch exposure to a ten per cent solution of Santicizer 140, was reported not to elicit any signs of a sensitization response. In an animal experiment reported in this paper, four rabbits were subject to patch testing using cresyl diphenyl phosphate (as Santicizer 140) resulting in slight irritancy. At challenge 14 days later, no evidence of a sensitizing effect was noted. From the extremely limited methodological detail reported, it is not possible to judge how the protocols used in the study compare with modern study designs such as the OECD test guidelines; however, it is likely that the methods would not be considered valid by current standards.

Thus, there is inadequate information to assess the sensitizing potential of cresyl diphenyl phosphate.

4.4.6 Repeated-dose toxicity

Animal data

Pharmaco LSR (1995, cited in BG Chemie 2000) investigated the effects of cresyl diphenyl phosphate following repeated oral gavage in a study conducted according to OECD test guideline 407 (GLP status not known). Doses used in the full 28-day study were based on results from a preliminary study in which CD rats (five/sex/group) received cresyl diphenyl phosphate (99.87 per cent pure with no *ortho*-isomer) in corn oil by oral gavage at doses of 0, 100, 300 or 1,000 mg/kg bw/day for seven days. In this preliminary investigation, there were no deaths and the only treatment-related effects were occasional salivation at the highest dose and lower weight gains in males of the high-dose group. Consequently in the main study, CD rats (five/sex/group) were

given cresyl diphenyl phosphate (99.87 per cent, free of *ortho*-isomer) in corn oil by oral gavage at doses of 0, 62.5, 250 and 1,000 mg/kg bw/day for 28 days. It is stated in BG Chemie (2000) that all investigations were carried out in accordance with the guideline, but gives no further details.

Following administration of the highest dose to rats in the main study, many effects were observed. BG Chemie (2000) does not present information on the magnitude or statistical significance of these changes or the numbers of animals affected. All effects are assumed to be in relation to the negative control group in which animals received corn oil only. Four males and two females died during the last week of treatment; at macroscopic examination one of the following abnormalities was found per animal: enlarged and pale kidneys; thickened wall of stomach or urinary bladder; abnormal contents of the urinary bladder (pale solid material); dark liver and dark foci in the lungs, bronchi and thymus gland. Histopathology of the animals that died revealed changes to the liver (diffuse hypertrophy), stomach (hyperkeratosis, acanthosis), kidneys (basophilic cortical tubuli, tubular dilatation, hyaline casts), adrenal glands (fatty vacuolisation) and urinary bladder (hyperplasia). In the 1,000 mg/kg bw/day group, other reported effects were: from day four of treatment, ungroomed coat, general hair loss in females, delayed bodyweight gain in males; reduced food consumption during the last week of treatment; and increased water consumption. On day 24 of treatment, haematological investigations revealed reduced mean cell volume, marginally reduced packed cell volume, increased total leukocyte and lymphocyte counts and marginally low haemoglobin concentration (females only). Biochemical analysis of serum showed elevated creatinine levels, reduced chloride concentrations and changes in protein levels (elevated α-2 and β-globulin, lowered albumin). Females exhibited elevated calcium and phosphorus concentrations and aspartate aminotransferase activity while males showed increased alanine aminotransferase activity. After 22 days of treatment, animals produced higher urinary volumes of slightly low specific gravity. Urinary protein content was slightly increased and urinary sediments were found to contain epithelial cells and leucocytes. At necropsy, there was an increase in absolute and relative liver, kidney and adrenal weights. Histopathology revealed changes in the renal tubules (basophilic cortical tubules, tubular dilatation, hyaline casts), liver (diffuse hypertrophy) and adrenals (cortical fatty vacuolation).

In the 250 mg/kg bw/day group, fewer adverse effects were observed. There were no deaths. In females there was slightly increased water consumption. Biochemical serum analysis showed changes in protein level (elevated α -2 and β -globulin, lowered albumin), and after 22 days of treatment animals had increased urinary protein and urinary sediments (containing epithelial cells and leucocytes). At necropsy, absolute and relative liver weights were higher in males. Histopathological changes in the renal tubules (basophilic cortical tubules, tubular dilatation, hyaline casts) of males and liver hypertrophy in both sexes were noted.

In the 62.5 mg/kg bw/day group, only marginal changes in protein concentrations (elevated α -2 and β -globulin, lowered albumin) were observed. Therefore this dose was concluded to be the no observed adverse effect level (NOAEL) for this study.

In an OECD test guideline 422 study, ‘Repeat dose and reproductive/developmental screening toxicity test’ (MHW, Japan 1993a; a Japanese language paper with English summary for which additional details are reported from secondary sources (UNEP 2002 and BG Chemie 2000)), conducted to GLP, male and female Sprague-Dawley rats (ten per group) were administered 0, 12, 60 or 300 mg/kg bw/day CPDD (technical grade; 41.9 per cent purity without any *ortho*-isomer, or tri-*o*-cresyl phosphate) in olive oil by oral gavage. Males were dosed for 45 days, including a 14-day period prior to mating. Females were dosed for 14 days before mating until day three of lactation. The doses used were reported to be based on results from a two-week preliminary study (original reference not identified), in which doses of 500 and 1,000 mg/kg bw/day were

found to be toxic (effects included reduced motility, ataxia, salivation, slow respiration, death and increased liver and adrenal weights), and important reproductive effects were noted (testicular atrophy in males and failure of females to become pregnant, BG Chemie 2000). Details of the reproductive and developmental toxicity aspects of the study are reported in Section 4.4.9. The following sub-acute toxic effects were noted in the treated rats, although the secondary literature source used provided no information on the magnitude or statistical significance of the changes.

At 300 mg/kg bw/day, bodyweight gain was reduced while food consumption (males only up to study day 28) and water intake were increased. Haematology and blood chemistry examinations were performed only in male animals. Blood chemical examination showed lower cholinesterase activities in the brain, serum and erythrocytes, higher glutamyl pyruvic transaminase (GPT) activity and levels of γ--GTP, total cholesterol and calcium, and lower glutamyl oxaloacetic transaminase (GOT) activity and levels of albumin, albumin/globulin (A/G) ratio and triglyceride. Urinalysis revealed lower pH and specific gravity and higher urine volume. At necropsy, the high-dose animals had higher relative liver, kidney (male only) and adrenal weights. Histopathological examination revealed enlargement and cortical vacuolation of the adrenals, enlargement of the liver, and fatty change in the proximal tubular epithelium. In addition, males showed a reduction in fatty changes of the hepatocytes and the presence of hyaline droplets and basophilic changes in the proximal tubular epithelium, erosion or focal necrosis of the stomach mucosa, atrophy of the seminiferous tubules and degeneration of the germinal epithelium. Females had clear cell change of hepatocytes, atrophy of the thymus, and hypertrophy and hyperplasia of the interstitial cell in the ovaries (UNEP 2002 and BG Chemie 2000).

In the group given 60 mg/kg bw/day, bodyweight gain was slightly lower in females and food consumption was higher in males until study day seven. Total cholesterol was increased and enlargement and cortical vacuolation of the adrenals were found in both sexes. In addition, enlargement of the liver was found in males, and histopathological changes in the liver (clear cell changes), kidneys (fatty change of the proximal tubular epithelium) and the thymus (atrophy) were noted in females (UNEP 2002 and BG Chemie 2000). The cholinesterase activities of the serum, erythrocytes and brain showed a significant, dose-related reduction in the high- and mid-dose groups (UNEP 2002 and BG Chemie 2000).

The NOAEL for the sub-acute toxicity component of this study was 12 mg/kg bw/day (MHW, Japan 1993a, cited in UNEP 2002), and is considered to be the overall NOAEL for cresyl diphenyl phosphate.

Cresyl diphenyl phosphate (purity not known, but thought to contain the *ortho*-isomer) in olive oil was applied to the shaved skin (3 cm^2 exposed area, position not stated) of groups of four guinea pigs (strain and sex not given) daily for 73 days. Administered doses were equivalent to approximately 120, 240, 480, 720 or 960 mg/kg bw/day. A control group of four animals was given the vehicle, olive oil. Two animals from each of the two highest dose groups died during the last week of treatment. All guinea pigs, including those in the control group, showed slight erythema with scale formation; this was attributed to the presence of the vehicle, olive oil. There was a dose-dependent increase in alopecia from 240 mg/kg bw/day, and bodyweight gains were reduced in the two highest doses. At 480 mg/kg bw/day, hind limb paralysis was observed in two animals. At doses greater than 480 mg/kg bw/day, paralysis of the hind limbs and lower portions of the back muscles were observed in all animals (the time of onset of signs of paralysis were not given). At examination of the spinal cord at necropsy of those guinea pigs with paralysis, the most prominent change was oedema of the white matter, particularly in the ventral funiculus, and bleeding in the grey zone. Effects on the liver were apparent from 480 mg/kg bw/day, and included excess blood flow, an increase in collagen fibres in the sinusoids, disseminated large drop-like lipid infiltration

and moderate glycogen depletion. At 720 mg/kg bw/day, the severity of hepatic effects increased, with changes including massive terminal hyperaemia with intralobular bleeding, considerable glycogen depletion and medium to large drop-like central intermediary fatty infiltration. The highest dose caused all of these effects plus necrosis of hepatocytes and complete glycogen depletion. At doses of 480 mg/kg bw/day or above, hyperplasia, formation of fatty cysts, lipid vacuoles in the cortex and hyperaemia in the cortex and medulla of the adrenal glands were noted. The NOAEL for this study was considered to be the lowest dose tested; 120 mg/kg bw/day (Geffke *et al*. 1970, cited in BG Chemie 2000, UNEP 2002).

Neurotoxicity

Many studies relating to the potential neurotoxic effects of cresyl diphenyl phosphate have been identified. However, care is needed in interpreting these studies and the relevance of many of the studies to current cresyl diphenyl phosphate formulations on the market is questionable. According to BG Chemie (2000), only the *ortho*-cresyl isomer of cresyl diphenyl phosphate or technical grade cresyl diphenyl phosphate mixtures containing the *ortho*-cresyl isomer appear to be neurotoxic. This has been attributed to the *ortho*-isomer being the only isomeric form capable of undergoing metabolism to phenyl saligenin phosphate, which is thought to be responsible for the neurotoxic effects observed in some studies. In order to form this metabolite, the phenyl ring must have an *ortho*-alkyl substituent and the α-carbon atom of the *ortho*-alkyl group must possess at least one hydrogen atom. The underlying mechanism is thought to involve phosphorylation of neuropathy target esterase by the phenyl saligenin phosphate, then enzyme-substrate complex ionisation by hydrolysis of the ester group, leading to inactivation or 'aging' of the enzyme. As cresyl diphenyl phosphate products currently on the market in the EU contain the *ortho*-cresyl isomer only at levels below 0.02 per cent (Bayer 2002), only studies that tested *ortho*-isomer-free forms of cresyl diphenyl phosphate have been considered in this assessment.

There are no publicly available studies conducted to OECD test guidelines specifically designed to investigate neurotoxicity (such as OECD test guideline 418 or 419).

In the study conducted to OECD test guideline 407 described in detail above (conducted by Pharmaco:LSR 1995, cited in BG Chemie 2000), no clinical signs of neurotoxicity were observed when cresyl diphenyl phosphate (99.87 per cent pure with no *ortho*-isomer) was given to CD rats as gavage doses up to 1,000 mg/kg bw/day.

Johannsen *et al*. (1977) administered two doses of 10 g/kg bodyweight cresyl diphenyl phosphate (containing *meta*- and *para*-cresyl isomers only) by gavage to eight hens (strain uncertain but Leghorn stated in UNEP 2002) on study days one to three. The hens were observed for abnormal behaviour and subsequently given a further two doses each day on study days 21 to 23. Bodyweights were recorded on days 0, 21 and 42. Daily observation continued until study day 42 when sacrifice and gross pathological examination occurred. The brain, sciatic nerve and spinal cord were removed *in situ* and fixed in ten per cent buffered formalin. Haematoxylin-eosin stained sections of these tissues were examined microscopically. No signs of systemic toxicity, abnormal behaviour or histopathological anomalies were reported in any of the animals tested (Johannsen *et al*. 1977).

In a study reported by Bayer AG (1971, study report in German. therefore study details taken from BG Chemie 2000, UNEP 2002), hens (HNL; eight per group) were administered cresyl diphenyl phosphate (as Disflamoll DPK) in their diet for 30 days at concentrations of 0, 100, 300, 1,000 or 3,000 mg/kg feed (equivalent to approximately 0, 207, 607, 2,118 or 4,602 mg/kg bw/day). The hens were then observed for a further 28 days. Reduced bodyweight was observed in the highest dose group but no signs of neurotoxicity were noted in any of the animals.

Human data

No human data are available.

Summary and discussion of repeated - dose toxicity

There are no human data regarding the potential for cresyl diphenyl phosphate to cause adverse health effects following repeated exposure by any route.

There are no experimental animal data for effects following repeated inhalation of cresyl diphenyl phosphate.

Although drawn from secondary sources, there are adequate data from studies conducted to OECD test guidelines to characterise the toxicity of cresyl diphenyl phosphate following repeated oral gavage exposure at doses up to 1,000 mg/kg bw/day. Evidence of repeat dose toxicity included increased salivation, suppression in bodyweight gain and increases in water intake and food consumption. Haematological examination of males has shown anaemia and an increase of leukocytes. Blood chemical examination showed a decrease of cholinesterase activities in the brain, serum and erythrocytes, increases in GPT, γ-GTP, total cholesterol and calcium, and decreases in GOT, albumin, A/G ratio and triglycerides in the 300 mg/kg bw/day group of males. At urinalysis, decreases in pH and specific gravity and an increase in urine volume have been reported. Histopathological examination showed changes in the adrenals, liver, kidneys, stomach, testes, thymus and ovaries. The overall NOAEL for repeated dose toxicity is considered to be 12 mg/kg bw/day, which is the lowest NOAEL obtained from the two good quality guideline oral studies (Pharmaco:LSR 1995 (cited in BG Chemie 2000) and MHW, Japan 1993a (cited in UNEP 2002)).

The cresyl diphenyl phosphate products currently marketed in the EU have less than 0.02 per cent ortho-cresyl isomer content, and are not expected to cause neurotoxicity. Although the neurotoxicity studies were not conducted in accordance with OECD test guidelines and acetylcholinesterase and neuropathy target esterase (NTE) enzyme activities were not measured, the evidence suggests that neither isomer will cause delayed neuropathy at doses below those at which other effects (overall NOAEL 12 mg/kg bw/day) are observed.

4.4.7 Mutagenicity

Studies in vitro

Genetic mutations

Several studies have investigated the potential for cresyl diphenyl phosphate to cause gene mutations *in vitro*. As far as can be deduced from secondary literature, one of these studies was conducted to the Japanese guideline for ‘screening mutagenicity testing of chemicals’, and the others were conducted using protocols approximating to OECD guidelines, although there is insufficient information in the secondary sources to confirm the extent of similarity.

In a bacterial reverse mutation assay conducted to Japanese guidelines and GLP, cresyl diphenyl phosphate (commercial purity: 41.9 per cent) was tested in *Salmonella typhimurium* strains TA 98, 100, 1535 and 1537, as well as *E.coli* WP2uvrA, with and without metabolic activation (rat liver induced with phenobarbital and 5,6-benzoflavone). The concentrations of cresyl diphenyl phosphate tested were 0 (DMSO

only), 312, 625, 1,250, 2,500 and 5,000 µg per plate in DMSO solvent (three plates per test, incubated for 20 minutes at 37 °C, two replications). Cytotoxicity was observed with and without metabolic activation at the highest concentration tested, 5000 µg per plate. The positive controls were AF-2 (TA 100, TA 98 and WP2uvrA), sodium azide (TA 1535) and 9-aminoacridine (TA 1537) without S9, and 2-aminoanthracene (all strains) with S9. Results for the positive and negative controls were not described in the available summaries. No signs of mutagenicity were reported at any concentration of cresyl diphenyl phosphate with and without metabolic activation (MHW, Japan 1993b, cited in MHW Japan 1995).

UNEP (2002) and BG Chemie (2000) briefly summarise two similar standard-plate incorporation tests. In both tests *S. typhimurium* strains TA 98, 100, 1535 and 1537 were incubated with cresyl diphenyl phosphate at concentrations in the range 20 to 2,500 µg/plate (no further details) with and without metabolic activation (S9 from Aroclor 1254-induced rat liver). The test substance exhibited a dose-dependent bacteriotoxic effect from 20 µg/plate, with precipitation at the high dose of 2,500 µg/plate. Inclusion or otherwise of positive or negative controls were not mentioned in the summaries. There were no indications of mutagenic activity in either of the studies (Zeigler *et al*. 1987 and Bayer AG 1988, cited in UNEP 2002, BG Chemie 2000).

Chromosomal effects

Cresyl diphenyl phosphate (commercial purity: 41.9 per cent, with no detectable amounts of *ortho*-cresyl isomer) was tested for clastogenic activity in an *in vitro* mammalian chromosomal aberration test using Chinese hamster lung cells. The test was conducted in accordance with Japanese guidelines and to GLP, and the protocol used was similar to OECD test guideline 473, but there was insufficient information in the Japanese language and tertiary references to make a complete comparison. In a preliminary study, cytotoxic concentrations (50 per cent inhibition of cell proliferation) following a six-hour exposure period were 0.037 and 0.043 mg/ml, with and without metabolic activation respectively. When the exposure period was increased to 48 hours, the cytotoxic concentration was 0.016 mg/ml (BG Chemie 2000, MHW, Japan 1995). The main study was conducted with exposure periods of six, 24 and 48 hours. In the six-hour phase, concentrations of cresyl diphenyl phosphate used were 0.011, 0.022 or 0.043 mg/ml. In the absence of metabolic activation at all concentrations, and in the presence of activation at concentrations up to 0.022 mg/ml, there was no indication of chromosome damage or induction of polyploidy (800 cells per group analysed). An increase in the occurrence of chromosome damage, but no increase in the frequency of polyploidy, was noted in cells at the highest concentration in the presence of metabolic activation. However, the significance of these results is debatable as the highest dose employed was shown to be cytotoxic in the preliminary study. The extent of cytotoxicity was not reported for the main study but the low number of cells evaluated (93 for clastogenicity and 125 for polyploidy) at the highest concentration is a possible reflection of high cytotoxicity (see Table 4.7; BG Chemie 2000). MHW, Japan (1995) states that a confirmation test was conducted and that reproducibility was confirmed (see Table 4.8). The data presented indicate that the number of cells with aberrations increased in the absence of cytotoxicity.

Table 4.7 Chromosomal analysis of Chinese Hamster lung cells treated with cresyl diphenyl phosphate with metabolic activation for six hours*

Group	Concentration (mg/ml)	No. cells analysed	Total number of structural aberrations	Number of cells with aberrations (%)		Polyploidy (%)	Result	
				TAG	TA		Structural aberration	Numerical aberrations
Solvent	0	200	0	0 (0)	0 (0)	0.38	-	-
CDPP	0.011	200	6	4 (2)	2 (1)	0.25	-	-
CDPP	0.022	200	5	3 (1.5)	3 (1.5)	0.0	-	-
CDPP	0.043	93	19	8 (8.6) **	7 (7.5)**	1.6	Toxicity	Toxicity
Cyclophosphamide	0.005	200	428	144 (72)**	144 (72)**	0.0	+	-

Table 4.8 Chromosomal analysis of Chinese Hamster lung cells treated with cresyl diphenyl phosphate with metabolic activation for six hours – confirmation test*

Group	Concentration (mg/ml)	No. cells analysed	Total number of structural aberrations	Number of cells with aberrations (%)		Polyploidy	Result	
				TAG	TA		Structural aberration	Numerical aberrations
Solvent	0	200	4	4 (2)	2 (1)	0.38	-	-
CDPP	0.011	200	2	2 (1)	1 (0.5)	0.13	-	-
CDPP	0.022	200	6	5 (2.5)	3 (1.5)	0.25	-	-
CDPP	0.043	200	46	22 (11)**	20 (10)**	0.75	+	-
Cyclophosphamide	0.005	200	327	122 (61)**	166 (58)**	0.5	+	-

Source: *MHW, Japan (1995).
Notes: **Significantly different from the solvent control, $p<0.05$;
CDPP: Cresyl diphenyl phosphate, TAG: Total number of cells with aberrations, TA: Total number of cells with aberrations except gap.

Concentrations of 0.004, 0.008 and 0.016 mg cresyl diphenyl phosphate per ml tested in the absence of metabolic activation only for 24 and 48 hours did not show any chromosome-damaging effects (BG Chemie 2000). The negative and positive controls gave appropriate results under all test conditions.

Studies in vivo

MHW, Japan (1996a, Japanese paper with English language summary) summarises a mammalian erythrocyte micronucleus test conducted according to OECD test guideline 474 and GLP. In this study (MHW, Japan 1996b, cited in MHW, Japan 1996a), male and female Crj:BDF_1 mice (five per group) were given single oral gavage doses of 0 (olive oil only), 312, 625 or 1,250 mg/kg bw cresyl diphenyl phosphate (purity not known) in olive oil. Cyclophosphamide at a dose of 50 mg/kg bodyweight was used as the positive control but no information regarding the negative or positive control results was reported. The lowest observed adverse effect level (LOAEL) for the study was 1,250 mg/kg bodyweight and the maximum tolerated dose for males and females was above 1,250 and 1,250 mg/kg bodyweight, respectively (no further information given). The frequency of micronucleated erythrocytes was not significantly increased in male or female mice at doses up to 1,250 mg/kg bodyweight at 24 hours after treatment. Inhibition of bone marrow cell proliferation was not observed under the conditions of this study (MHW Japan 1996b, cited in MHW, Japan 1996a).

BG Chemie (2000) also summarises a mammalian erythrocyte micronucleus test, which appears to have been conducted to OECD test guideline 474, but there is insufficient information in the secondary source to fully confirm this. In this study, male and female NMRI mice were given a single intraperitoneal dose of cresyl diphenyl phosphate (99.9 per cent pure with no *ortho*-isomer) in corn oil. Doses of 0 (corn oil only), 100, 300 or 1,000 mg/kg bodyweight were given on the basis of a preliminary toxicity study in which 1,000 mg/kg bodyweight was found to be the highest tolerable dose (no reference provided). After 16 hours (1,000 mg/kg bodyweight), 24 hours (100, 300 or 1,000 mg/kg bodyweight) or 48 hours (1,000 mg/kg bodyweight), a sample of bone marrow was taken from the femoral bone of five male and female animals per dose and the ratio of polychromatic to normochromatic erythrocytes was determined; the number of micronucleated polychromatic erythrocytes was also counted. For each sample, 1,000 cells were scored. No information was reported on the findings for the positive and negative control groups. Animals in the highest dose group had depressed spontaneous activity, closed eyelids and convulsions, and one animal died. In this group, the number of normochromatic erythrocytes was slightly increased (1,033 versus 721 in negative control group) after 24 hours but this was interpreted as a cytotoxic effect. There were no increases in micronucleated polychromatic erythrocytes in any of the treated groups..It was concluded that cresyl diphenyl phosphate did not cause chromosome damage in this study (CCR 1993, cited in BG Chemie 2000).

Summary of mutagenicity

Based on several valid gene mutation assays using *S. Typhimurium,* cresyl diphenyl phosphate is not a bacterial gene mutagen. In an *in vitro* mammalian chromosomal aberration test using Chinese hamster lung cells conducted to Japanese test guidelines (similar to OECD test guideline 473), cresyl diphenyl phosphate caused structural chromosomal damage in Chinese hamster lung cells with metabolic activation following short-term incubation (six hours). However, there was no evidence of chromosomal damage with longer incubations (24 and 48 hours – no metabolic activation only) or after six-hour incubation without metabolic activation, and the influence of cytotoxicity on the positive finding is not clear (BG Chemie 2000, MHW, Japan 1995).

Cresyl diphenyl phosphate did not cause chromosomal aberrations in two valid *in vivo* guideline (OECD test guideline 474) mammalian erythrocyte micronucleus tests. On the basis of these results, cresyl diphenyl phosphate is not expected to be an *in vivo* mutagen (MHW, Japan 1996b (cited in UNEP 2002) and CCR 1993 (cited in BG Chemie 2000).

The negative *in vitro* gene mutation assays, and two negative *in vivo* chromosomal aberration studies, provide reassurance that, despite the positive result in one *in vitro* chromosomal aberration study, cresyl diphenyl phosphate is not likely to be a mutagen *in vivo*.

4.4.8 Carcinogenicity

There are no data on the carcinogenic potential of cresyl diphenyl phosphate.

4.4.9 Toxicity to reproduction

Fertility and reproductive toxicity

The study conducted to OECD test guideline 422 'Repeat dose and reproductive/ developmental screening toxicity test' (MHW, Japan 1993a, a Japanese language paper with an English summary; additional details were taken from secondary sources, UNEP 2002 and BG Chemie 2000) described in Section 4.4.6, is adequate to assess the potential for cresyl diphenyl phosphate to cause adverse effects on fertility and reproduction. Available methodological details are summarised above and will not be repeated here. The effects on reproductive health were all observed at the highest dose in the presence of general systemic toxicity (see Section 4.4.6). In male rats, the effects were atrophy of the testicular seminiferous tubules (9 out of 10 animals) accompanied by reduced sperm count and degeneration of the germinal epithelium (evidence of reduced fertility). In females, six non-pregnant females without parturition exhibited ovarian interstitial cell hypertrophy and hyperplasia and reduced implantation and delivery rates (no further information available). There were no treatment-related adverse effects on copulation rates, gestation length, number of corpora lutea, delivery index or maternal behaviour. Observation of the neonates did not reveal any significant treatment-related adverse effects on the number of live offspring, sex ratio, general condition or bodyweight. The NOAEL for reproductive toxicity in parental rats was 60 mg/kg bw/day based on the reduced fertility (attributed to inhibition of spermatogenesis), and 300 mg/kg bw/day (the highest dose tested) for offspring.

Developmental toxicity

In the OECD test guideline 422 'Repeat dose and reproductive/developmental screening toxicity test' (MHW, Japan 1993a cited in UNEP 2002) described above and in Section 4.4.6, there were no reported effects on neonate development, particularly no skeletal or visceral malformations (no further information given). The NOAEL for developmental toxicity was 300 mg/kg bw/day (the highest dose tested).

In a study apparently conducted to OECD test guideline 414 'Prenatal developmental toxicity study' (insufficient information is given to judge whether this is the case), groups of 22 female CD rats received cresyl diphenyl phosphate (purity of 99.85 per cent, without any *ortho*-isomer) in corn oil by oral gavage, at doses of 0 (corn oil only), 100, 300 or 900 mg/kg bw/day on days six to 15 of gestation. On day 20 of gestation,

caesarean sections were conducted. Signs of toxicity in the high dose group dams were hair loss, piloerection, bodyweight stasis or loss, reduced food consumption, increased water intake, anaemia, leukocytosis, polychromasia and/or hypochromasia, high ß-globulin concentration and alanine and aspartate aminotransferase activities, and low albumin concentration, (no information on timeframes or magnitudes of effects given). At 300 mg/kg bw/day rats had reduced water consumption, anaemia, leukocytosis, low albumin concentration, and high β-globulin concentration. Only marginal signs of anaemia were reported for the low-dose group (no further information given). There were no reported treatment-related effects from the necropsy examinations. At all doses there were no adverse effects on fetal survival rates, growth and development *in utero* or other reproductive parameters and there were no teratogenic effects. The NOAEL for general toxicity in the dams was 100 mg/kg bw/day, and for developmental toxicity in the fetuses was 900 mg/kg bw/day (the highest dose tested) (Huntingdon Life Sciences 1996, cited in BG Chemie 2000).

Summary of toxicity to reproduction

In a study conducted to OECD test guideline 422, it was found that cresyl diphenyl phosphate caused inhibition of spermatogenesis and, consequently, decreased fertility, implantation rates, and lower delivery rates at the highest dose tested (300 mg/kg bw/day). However, these effects were only observed in the presence of systemic toxicity. No adverse effects on parameters relating to the neonates were reported. In addition, there were no adverse effects on development of the offspring at any dose (MHW, Japan 1993a cited in UNEP 2002).

In a study conducted to OECD test guideline 414, there were no adverse effects on fetal development up to doses of 900 mg/kg bw/day (Huntingdon Life Sciences 1996, cited in BG Chemie 2000).

4.4.10 NOAEL and Margins of Safety (MOS) for assessment of human exposure via the environment

There are no data on the carcinogenic potential of cresyl diphenyl phosphate. Based on several valid gene mutation assays, cresyl diphenyl phosphate is not a bacterial gene mutagen. The weight of evidence also suggests that cresyl diphenyl phosphate is not clastogenic or an *in vivo* mutagen.

In studies conducted to OECD test guidelines, cresyl diphenyl phosphate has been shown to cause adverse effects on reproductive performance only in the presence of systemic toxicity. However, it cannot be assumed that the reproductive toxicity is a secondary non-specific consequence of the other effects. No evidence of developmental toxicity has been reported.

The critical study chosen for derivation of a NOAEL for cresyl diphenyl phosphate (MHW, Japan 1993a, cited in UNEP 2002) was a good quality repeated dose toxicity study which provides the lowest NOAEL within the dataset. In this OECD repeat dose and reproductive/developmental screening toxicity test, male and female rats were administered 0, 12, 60 or 300 mg/kg bw/day cresyl diphenyl phosphate by oral gavage. Males were dosed for 45 days, including 14 days prior to mating. Females were dosed for 14 days before mating, and then through until day three of lactation. Administration of 300 mg/kg bw/day resulted in enlargement and cortical vacuolation of the adrenals, enlargement of the liver and fatty changes of the proximal tubular epithelium in both sexes. In males, 300 mg/kg bw/day also resulted in reduction of fatty change of the hepatocytes, hyaline droplets and basophilic changes in the renal proximal tubular epithelium, and erosion, focal necrosis and atrophy of seminiferous tubules. In females,

clear cell change of hepatocytes, atrophy of the thymus, hypertrophy and hyperplasia of the interstitial cells in the ovaries were observed in those given 300 mg/kg bw/day. In the intermediate dose group, which was given 60 mg/kg bw/day, enlargement and cortical vacuolation of the adrenals were found in both sexes. In addition, increased food consumption and total cholesterol (no further details), decreased cholinesterase activities (no further details), and hepatic enlargement were found in male rats; suppression of bodyweight gain, and histopathological changes (not precisely specified in UNEP 2002) in the liver, kidneys and the thymus were found in female rats. No effects relevant to reproduction were observed. This study, conducted to OECD test guidelines, identified a NOAEL of 12 mg/kg bw/day for cresyl diphenyl phosphate.

No neurotoxicity was observed in hens given cresyl diphenyl phosphate in their diet up to concentrations of 3,000 mg/kg for 30 days (Bayer AG 1971, cited in UNEP 2002).

A margin of safety of at least 600-fold is considered to be sufficient to protect against effects on humans through the environment. This is made up of uncertainty factors for interspecies variation (10), intraspecies variation (10) and extrapolation from a 45-day study to chronic (6).

A number of possible areas for clarification in the mammalian toxicity data base are listed in Appendix 1.

4.4.11 Derivation of PNEC for secondary poisoning

For cresyl diphenyl phosphate, a NOAEL of 12 mg/kg bw/day for male rats was established based on a 45-day repeat dose reproductive/developmental screening toxicity test. The TGD recommends a conversion factor of 20 based on rats older than six weeks to convert from a NOAEL to a NOEC, which would result in a NOEC of 240 mg/kg diet. The TGD recommends an assessment factor of 300 for extrapolation of a mammalian toxicity test of 28 days duration, and this is deemed the most appropriate assessment factor in this instance.

Based on these values, a $PNEC_{oral}$ of 240/300 = 0.80 mg/kg can be calculated.

An avian 28-day neurotoxicity study on HNL hens was considered suitable for derivation of a $PNEC_{oral}$ for birds. A NOEL/NOEC of 1,000 mg/kg diet was established. The TGD recommends an assessment factor of 30 for extrapolation of a chronic avian toxicity test or 3,000 for an acute LC_{50} five day study, neither of which are deemed appropriate in this case since the study length is sub-chronic. Consequently, under a strict interpretation of the TGD, it is not possible to derive a definitive PNEC. An indicative 'provisional' value was therefore derived using an assessment factor of 300, this factor being recommended in the TGD as suitable for extrapolation of a mammalian study of 28 days duration.

Based on this, a provisional $PNEC_{oral}$ of 1,000/300 = 3.3 mg/kg can be calculated.

The TGD recommends that the lower $PNEC_{oral}$ (0.80 mg/kg) be taken forward for assessment of secondary poisoning, and so this value is used in this report.

4.5 Hazard classification

4.5.1 Classification for human health

Cresyl diphenyl phosphate is not currently classified in Annex I of Directive 67/548/EEC. According to the criteria of the EU, cresyl diphenyl phosphate does not need to be classified on the basis of its acute toxicity, skin or eye irritation potential, corrosivity to the skin or eyes, mutagenicity, or developmental toxicity.

There is a lack of data with which to assess the skin-sensitizing potential of the substance and thus it is not possible to make recommendations on classification for this endpoint.

It is difficult to judge whether the effects observed below the cut-offs for repeated dose classification are of sufficient severity to justify Xn R48, because only a brief description of the findings (notably the liver and kidney histopathological changes) in the key study (MHW 1993a) are available.

A Category 2 R60 classification is appropriate for effects on fertility, because a clear-cut effect has been observed in an animal model and there is supporting evidence on the site of action (spermatogenesis).

4.5.2 Classification for the environment

Current classification

Cresyl diphenyl phosphate is not currently classified in Annex I of Directive 67/548/EEC. A commercial cresyl diphenyl phosphate product appears to be currently classified as dangerous for the environment and carries the following hazard labelling (Bayer 2002):

N:	Dangerous for the environment.
R51/53:	Toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment.

Another commercial cresyl diphenyl phosphate product appears to be currently classified as dangerous for the environment and carries the following hazard labelling (Great Lakes Chemical Corporation 2002):

N:	Dangerous for the environment.
R50/53:	Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment.

The reason behind the different classifications is not clear.

Proposed classification

The bioconcentration factor (BCF) for cresyl diphenyl phosphate is around 200 l/kg. No fully valid acute toxicity studies are available for cresyl diphenyl phosphate with either fish or invertebrates. The predicted acute L(E)C_{50} for fish and *Daphnia magna* are around 1.2 and 1.6 mg/l respectively. There are non-standard algal studies available for cresyl diphenyl phosphate, and 4-hour IC_{50}s of 0.5 to 1.0 mg/l have been

determined for primary production. Based on the BCF and the data available from non-standard algal tests, the following classification could be considered:

N: Dangerous for the environment.

R50/53: Very toxic to aquatic organisms. May cause long-term adverse effects in the aquatic environment.

4.6 PBT assessment

The criteria for persistence (P and vP), bioaccumulation potential (B and vB) and toxicity (T) included in the TGD are shown in Table 4.9.

Table 4.9 Criteria for identification of PBT and vPvB substances

Criterion	PBT criteria	vPvB criteria
P	Half-life above 60 days in marine water or above 40 days in freshwater* or half-life above 180 days in marine sediment or above 120 days in freshwater sediment*	Half-life above 60 days in marine water or freshwater or above180 days in marine or freshwater sediment
B	BCF above 2,000	BCF above 5,000
T	Chronic NOEC below 0.01 mg/l or classification for certain human health end points, or endocrine disrupting effects	Not applicable

Notes: * For the purpose of marine environment risk assessment, half-life data in freshwater and freshwater sediment can be overruled by data obtained in marine conditions.

Persistence: cresyl diphenyl phosphate is readily biodegradable (Section 3.1.1). It does not therefore meet the P criterion.

Bioconcentration: a value of 200 was selected from the available data in Section 3.1.3. Hence, the substance does not meet the B criterion.

Toxicity: the lowest estimated NOEC is 0.014 mg/l. On this basis the substance does not meet the T criterion. A proposed classification as a Category 2 reprotoxin is made in Section 4.5.2. This would trigger the T criterion.

The overall conclusion is that the substance does not meet the PBT criteria.

5 Risk characterisation

This section identifies the potential risks that cresyl diphenyl phosphate might pose for the freshwater and marine aquatic compartments, terrestrial compartment, air compartment and predatory organisms through secondary poisoning. The risk characterisation is performed by comparing the PECs with the PNECs to derive a risk characterisation ratio (RCR). An RCR of less than one implies that any risk resulting from that level of exposure is acceptable. An RCR above one implies a potential risk, and all such values are highlighted in bold in the following tables. Annex C considers the effect of a faster hydrolysis rate on the overall conclusions.

As discussed in Section 3.1.2, the adsorption potential of the substance (represented by the K_{oc}) is estimated, and this has a significant influence on its predicted partitioning behaviour in the environment. There is some evidence for triphenyl phosphate (see the risk evaluation report of that substance in this series) that the prediction method might underestimate the K_{oc} for this type of substance. A sensitivity analysis has been performed in Annex D, and this shows that a higher K_{oc} value would affect the conclusions, but not necessarily in a straightforward (or especially significant) way. Further testing for sediment sorption coefficient is suggested for triphenyl phosphate, and this could indicate a need for further studies with this substance.

5.1 Aquatic compartment

5.1.1 Surface water

A PNEC for surface water was estimated as 1.4 μg/l. The resulting PEC/PNEC ratios are summarised in Table 5.1.

Table 5.1 Summary of risk characterisation ratios for surface water

Scenario		PEC (μg/l)	Risk characterisation ratio
Production of cresyl diphenyl phosphate		0.41 and 0.13	0.30 and 0.09
Textile/fabric coating	Compounding	0.38	0.27
	Application of coating	0.78	0.56
	Combined compounding/ application	1.05	0.75
Thermosets and epoxy resins	Compounding	1.12	0.80
	Conversion	0.45	0.32
	Combined compounding and conversion	1.45	**1.04**
Adhesives		negligible	negligible
Lubricant additive	Blending of lubricant	0.12	0.09
PVC – 1	Compounding	0.78	0.56
	Conversion	1.79	**1.28**
	Combined compounding and conversion	2.46	**1.76**
PVC – 2	Compounding	0.61	0.44
	Conversion	0.95	0.68
	Combined compounding and conversion	1.45	**1.04**

Table 5.1 continued.

Scenario		PEC (μg/l)	Risk characterisation ratio
PVC – 3	Compounding	1.72	**1.23**
	Conversion	2.80	**2.0**
	Combined compounding and conversion	4.42	**3.15**
PVC – 4	Compounding	0.61	0.44
	Conversion	0.28	0.20
	Combined compounding and conversion	0.78	0.56
PVC – 5	Compounding	0.61	0.44
	Conversion	0.28	0.20
	Combined compounding and conversion	0.78	0.56
PVC – 6	Compounding	0.61	0.44
	Conversion	0.95	0.68
	Combined compounding and conversion	1.45	**1.04**
Thermo-plastics and styrenics	Compounding	0.51	0.37
	Conversion	0.24	0.17
	Combined compounding and conversion	0.65	0.46
Polyurethane	Compounding	3.74	**2.67**
	Conversion	1.32	0.94
	Combined compounding and conversion	4.82	**3.44**
Regional sources		0.11	0.08

PEC/PNEC ratios are above one for the combined compounding and conversion step for some PVC applications, for polyurethane and for thermosets and epoxy resins. Potential risks are also identified for the compounding step for one PVC application and for polyurethanes, and for the conversion step for two PVC applications. Further information is needed on process emissions to refine the PECs for these scenarios. Information from two users of the substance indicates that floor washings and air extraction equipment washings are combined with other waters for treatment, but there is no information on the levels of cresyl diphenyl phosphate in these washings.

No risks to surface water are identified from the production sites, all three steps for thermoplastics and styrenics, textiles/fabric coating, two PVC scenarios, adhesives, use as a lubricant additive and regional sources based on the approach taken.

The sensitivity analysis in Annex C suggests that a faster hydrolysis rate than assumed here would only have a small impact on surface water concentrations.

There is some uncertainty over the PNEC for this endpoint (the derivation is based on an evaluation of the data across the group of aryl phosphate flame retardants). Further testing of members of the group is likely to be necessary to refine the assessments. However, this is most likely to involve sediment and terrestrial organisms rather than aquatic organisms. A long-term toxicity test on fish could therefore be considered for this substance to assess the reliability of the predicted value.

5.1.2 Waste water treatment

The PNEC for waste water treatment processes is above100 mg/l. The resulting risk characterisation ratios have been calculated, but are not summarised here as the ratios are below 0.01 for the production and all uses of cresyl diphenyl phosphate. On this basis, no risk to waste water treatment plants would be expected from the production and use of cresyl diphenyl phosphate.

5.1.3 Sediment

Both the exposure concentrations and the effect concentrations for sediment are derived from those for water by the equilibrium partition method. Hence, the risk characterisation ratios are the same as those for water, and the same comments apply.

5.2 Terrestrial compartment

The PNEC for soil is tentatively estimated as 0.059 mg/kg wet weight. The resulting risk characterisation ratios are summarised in Table 5.2.

PEC/PNEC ratios are above one for some scenarios, for use in one PVC application and for use in polyurethane. Further information on exposures identified for the aquatic compartment would also have an influence on the risk ratios here. The ratios are not very far above one and so further exposure data may remove the concerns.

Soil PECs are relatively insensitive to the soil degradation rate used (see Annex C).

Table 5.2 Summary of risk characterisation ratios for the terrestrial compartment

Scenario		PEC (mg/kg wet wt.)	Risk characterisation ratio
Production of cresyl diphenyl phosphate		negligible[a]	<0.01
Textile/fabric coating	Compounding	6.58×10^{-3}	0.11
	Application of coating	0.02	0.28
	Combined compounding and application of coating	0.02	0.39
Thermosets and epoxy resins	Compounding	0.02	0.41
	Conversion	8.24×10^{-3}	0.14
	Combined compounding and conversion	0.03	0.55
Adhesives		negligible	negligible
Lubricant additive	Blending of lubricant	3.96×10^{-4}	<0.01
PVC – 1	Compounding	0.02	0.28
	Conversion	0.04	0.69
	Combined compounding and conversion	0.06	0.97
PVC – 2	Compounding	0.01	0.21
	Conversion	0.02	0.35
	Combined compounding and conversion	0.03	0.55

Table 5.2 continued.

Scenario		PEC (mg/kg wet wt.)	Risk characterisation ratio
PVC – 3	Compounding	0.04	0.66
	Conversion	0.07	**1.11**
	Combined compounding and conversion	0.11	**1.77**
PVC – 4	Compounding	0.01	0.21
	Conversion	4.13×10^{-3}	0.07
	Combined compounding and conversion	0.02	0.28
PVC – 5	Compounding	0.01	0.21
	Conversion	4.16×10^{-3}	0.07
	Combined compounding and conversion	0.02	0.28
PVC – 6	Compounding	0.01	0.21
	Conversion	0.02	0.35
	Combined compounding and conversion	0.03	0.55
Thermo-plastics and styrenics	Compounding	9.86×10^{-3}	0.17
	Conversion	3.34×10^{-3}	0.06
	Combined compounding and conversion	0.01	0.22
Polyurethane	Compounding	0.09	**1.49**
	Conversion	0.03	0.5
	Combined compounding and conversion	0.12	**1.93**
Regional sources	Agricultural soil	3.44×10^{-5}	<0.01
	Natural soil	3.91×10^{-5}	<0.01
	Industrial soil	5.01×10^{-3}	0.08

Notes: a) Sewage sludge from the production sites is not spread onto land.

Toxicity data for terrestrial organisms would allow a PNEC to be derived directly, rather than through equilibrium partitioning.

5.3 Atmosphere

No information is available on the toxicity of cresyl diphenyl phosphate to plants and other organisms exposed via air. The low vapour pressure of the substance means that volatilisation to the atmosphere is likely to be limited and the resulting concentrations are likely to be low (predicted concentrations are all below 7×10^{-5} mg/m^3). The possibility of cresyl diphenyl phosphate contributing to atmospheric effects such as global warming and acid rain is thus likely to be small. In addition, as the substance does not contain halogen atoms, it will not contribute to ozone depletion.

5.4 Secondary poisoning

The PNEC for secondary poisoning is estimated as 0.8 mg/kg food. The resulting risk characterisation ratios are summarised in Table 5.3.

Table 5.3 Summary of risk characterisation ratios for secondary poisoning

Scenario		Fish food chain		Earthworm food chain	
		PEC (mg/kg)	PEC/PNEC	PEC (mg/kg)	PEC/PNEC
Production of cresyl diphenyl phosphate		0.05 and 0.02	0.06 and 0.03	negligible[a]	<0.01
Textiles/ fabric coating	Compounding	0.02	0.03	0.02	0.02
	Application of coating	0.02	0.03	0.04	0.05
	Combined compounding and application	0.03	0.03	0.06	0.07
Thermosets and epoxy resins	Compounding	0.05	0.07	0.06	0.08
	Conversion	0.03	0.04	0.02	0.03
	Combined compounding and conversion	0.06	0.08	0.08	0.1
Adhesives		negligible	negligible	negligible	negligible
Lubricant additive	Blending of lubricant	0.02	0.03	1.21×10^{-3}	<0.01
PVC – 1	Compounding	0.08	0.1	0.04	0.05
	Conversion	0.16	0.2	0.1	0.13
	Combined compounding and conversion	0.22	0.27	0.15	0.18
PVC – 2	Compounding	0.06	0.08	0.03	0.04
	Conversion	0.09	0.11	0.05	0.07
	Combined compounding and conversion	0.13	0.17	0.08	0.1
PVC – 3	Compounding	0.16	0.19	0.10	0.13
	Conversion	0.24	0.3	0.17	0.21
	Combined compounding and conversion	0.38	0.47	0.27	0.33
PVC – 4	Compounding	0.02	0.03	0.03	0.04
	Conversion	0.02	0.03	0.01	0.01
	Combined compounding and conversion	0.02	0.03	0.04	0.05
PVC – 5	Compounding	0.02	0.03	0.03	0.04
	Conversion	0.04	0.05	0.01	0.01
	Combined compounding and conversion	0.08	0.1	0.04	0.05
PVC – 6	Compounding	0.02	0.03	0.03	0.04
	Conversion	0.11	0.13	0.05	0.07
	Combined compounding and conversion	0.13	0.17	0.08	0.1
Thermo-plastics and styrenics	Compounding	0.02	0.03	0.03	0.03
	Conversion	0.04	0.04	8.66×10^{-3}	0.01
	Combined compounding and conversion	0.07	0.08	0.03	0.04

Table 5.3 continued.

Scenario		Fish food chain		Earthworm food chain	
		PEC (mg/kg)	PEC/PNEC	PEC (mg/kg)	PEC/PNEC
Poly-urethane	Compounding	0.32	0.4	0.22	0.28
	Conversion	0.12	0.15	0.08	0.09
	Combined compounding and conversion	0.41	0.51	0.29	0.36

Notes: a) Sewage sludge from the production sites is not spread onto land.

PEC/PNEC ratios are all below one. This indicates a low risk of secondary poisoning from production and all the current uses of cresyl diphenyl phosphate.

5.5 Risk characterisation for human exposure via the environment

A NOEL of 12 mg/kg bw/day in rats was identified in Section 4.4.10 as the most appropriate value for use in this assessment. A margin of safety of at least 600 is considered necessary to provide sufficient reassurance against effects on human health with this result (see Section 4.4.10). The estimated human exposures via the environment were calculated in Section 3.3.4 and are included in Table 5.4 together with the resulting margins of exposure.

All of the margins of safety are well above the required value, and so no risks are indicated for any scenario.

5.6 Marine risk assessment

Although a PEC/PNEC approach can be applied to the marine environment, there are additional concerns which may not be adequately addressed using the above methods. Chief among these concerns is the possibility that hazardous substances may accumulate in parts of the marine environment. The effects of such accumulation are unpredictable in the long term, and once such accumulation has occurred it may be practically difficult to reverse. The properties which lead to substances behaving in this way also lead to greater uncertainty in estimating exposures and/or effect concentrations, and so make a quantitative risk assessment more difficult. In order to identify substances which are likely to behave in this way, criteria have been developed relating to the persistence, accumulation and toxicity of the substance. The first part of the marine assessment is therefore a comparison of the properties of the substance with these criteria. This is presented in Section 4.6.

PEC values for the marine assessment are presented in Sections 3.3.1 and 3.3.4. These have been calculated using EUSES. PNECs for marine aquatic species are included in Section 4.1.6. The PNEC for secondary poisoning for the marine environment is the same as that for the freshwater fish and terrestrial food chains (Section 4.4.11). The resulting PEC/PNEC ratios are in Table 5.5.

Table 5.4 Margin of exposure

Scenario		Total daily human intake (mg/kg bw/day	Margin of exposure
Production of cresyl diphenyl phosphate		1.43×10^{-4} and 4.62×10^{-5}	83,920 and 259,740
Textile/fabric coating	Compounding	1.88×10^{-4}	63,830
	Application of coating	4.45×10^{-4}	26,970
	Combined compounding and application of coating	5.94×10^{-4}	20,200
Thermoplastics and styrenics	Compounding	2.58×10^{-4}	46,510
	Conversion	3.09×10^{-4}	38,840
	Combined compounding and conversion	7.26×10^{-4}	16,530
Adhesives		negligible	-
Lubricant additive	Blending of lubricant	4.96×10^{-5}	241,940
PVC – 1	Compounding	5.87×10^{-4}	20,440
	Conversion	2.96×10^{-3}	4,050
	Combined compounding and conversion	3.5×10^{-3}	3,430
PVC – 2	Compounding	6.05×10^{-4}	19,830
	Conversion	1.5×10^{-3}	8,000
	Combined compounding and conversion	2.06×10^{-3}	5,830
PVC – 3	Compounding	1.85×10^{-3}	6,490
	Conversion	4.71×10^{-3}	2,550
	Combined compounding and conversion	6.51×10^{-3}	1,843
PVC – 4	Compounding	$3.23\times10-4$	37,150
	Conversion	$1.38\times10-4$	86,960
	Combined compounding and conversion	$4.22\times10-4$	28,440
PVC – 5	Compounding	$3.12\times10-4$	38,460
	Conversion	$3.77\times10-4$	31,830
	Combined compounding and conversion	$8.97\times10-4$	13,380
PVC – 6	Compounding	$3.12\times10-4$	38,460
	Conversion	$1.72\times10-3$	6,980
	Combined compounding and conversion	$2.06\times10-3$	5,830
Thermosets and epoxy resins	Compounding	$8.01\times10-4$	14,980
	Conversion	$3.71\times10-4$	32,350
	Combined compounding and conversion	$1.13\times10-3$	10,620
Polyurethane	Compounding	4.1×10^{-3}	2,930
	Conversion	2.14×10^{-3}	5,610
	Combined compounding and conversion	6.1×10^{-3}	1,970
Regional sources		4.08×10^{-5}	294,120

Table 5.5 Summary of risk characterisation ratios for the marine compartment

Scenario		PEC/PNEC ratio			
		Local marine compartment	**Local marine sediment compartment**	**Fish-eating birds and mammals**	**Top predators**
Textile coating	Compounding	0.78	0.78	<0.01	<0.01
	Application of coating	**1.85**	**1.85**	<0.01	<0.01
	Combined compounding and application	**2.56**	**2.56**	<0.01	<0.01
Thermo-sets and epoxy resins	Compounding	**2.74**	**2.74**	0.02	<0.01
	Conversion	0.96	0.96	<0.01	<0.01
	Combined compounding and conversion	**3.63**	**3.63**	0.02	<0.01
Application		negligible	negligible	negligible	negligible
Lubricant additive	Blending of lubricant	0.11	0.11	<0.01	<0.01
PVC – 1	Compounding	**1.85**	**1.85**	0.03	<0.01
	Conversion	**4.52**	**4.52**	0.07	0.02
	Combined compounding and conversion	**6.3**	**6.3**	0.09	0.02
PVC – 2	Compounding	**1.41**	**1.41**	0.02	<0.01
	Conversion	**2.3**	**2.3**	0.03	<0.01
	Combined compounding and conversion	**3.63**	**3.63**	0.05	0.01
PVC – 3	Compounding	**4.34**	**4.34**	0.06	0.01
	Conversion	**7.19**	**7.19**	0.11	0.02
	Combined compounding and conversion	**11.5**	**11.5**	0.17	0.04
PVC – 4	Compounding	**1.41**	**1.41**	<0.01	<0.01
	Conversion	0.52	0.52	<0.01	<0.01
	Combined compounding and conversion	**1.85**	**1.85**	<0.01	<0.01
PVC – 5	Compounding	**1.41**	**1.41**	<0.01	<0.01
	Conversion	0.52	0.52	0.01	<0.01
	Combined compounding and conversion	**1.85**	**1.85**	0.03	<0.01
PVC – 6	Compounding	**1.41**	**1.41**	<0.01	<0.01
	Conversion	**2.3**	**2.3**	0.04	0.01
	Combined compounding and conversion	**3.63**	**3.63**	0.05	0.01

Table 5.5 continued.

Scenario		PEC/PNEC ratio			
		Local marine compartment	**Local marine sediment compartment**	**Fish-eating birds and mammals**	**Top predators**
Thermo-plastics and styrenics	Compounding	**1.14**	**1.14**	<0.01	<0.01
	Conversion	**0.43**	**0.43**	<0.01	<0.01
	Combined compounding and conversion	**1.49**	**1.49**	0.02	<0.01
Poly-urethane	Compounding	**9.68**	**9.68**	0.14	0.03
	Conversion	**3.27**	**3.27**	0.05	0.01
	Combined compounding and conversion	**12.5**	**12.5**	0.18	0.04

The production step is not included in these calculations as the production sites do not discharge to the marine environment.

Risks are indicated for most scenarios for marine waters and marine sediments (lubricant blending is the main exception). The regional concentrations in marine waters and sediments do not indicate a risk.

Further information on emissions from these processes indicated for the freshwater environment would also help to refine these results. More specifically for the marine assessment, information on whether any of these processes avoid discharging to the marine environment or do so only after effluent treatment (the calculations above assume a direct discharge to the marine environment without waste water treatment) would be useful.

Testing on freshwater organisms would also affect the marine PNEC. Testing on sediment organisms would be of more value for the sediment assessment. There is also the possibility of testing on marine species, which would allow the assessment factor to be reduced.

The size of the PEC/PNEC ratios suggests that no one part of the further information requirements would be sufficient on its own to reduce the ratios to below one.

No risks are indicated for marine predators.

6 Conclusions

Cresyl diphenyl phosphate can enter the environment from its production and use, and from the use of articles made from materials containing the substance. Based on the available information, potential risks are identified for all of the life cycle steps for one or more of the protection goals. The overall conclusions are summarised in Table 6.1 in a simplified form. In particular, the different steps in the use of each material have been combined here, and risks are indicated for PVC provided at least one of the different uses shows a risk for the specific protection goal. Section 5 should be consulted for the detailed results.

Table 6.1 Summarised potential environmental risks identified for cresyl diphenyl phosphate

Life cycle stage	Surface water	Sediment	WWTP	Air	Soil	Aquatic food chain	Terrestrial food chain	Marine water	Marine sediment
Production	-	-	-	-	-	-	-	-	-
Textile/fabric coating	-	-	-	-	-	-	-	✸	✸
Thermosets/epoxy resins	-	-	-	-	-	-	-	✸	✸
Adhesives	-	-	-	-	-	-	-	-	-
Lubricant additive	-	-	-	-	-	-	-	-	-
PVC	✸	✸	-	-	✸	-	-	✸	✸
Thermoplastics/styrenics	-	-	-	-	-	-	-	✸	✸
Polyurethane	✸	✸	-	-	✸	-	-	✸	✸
Regional	-	-	-	-	-	-	-	-	-

There are no risks for humans exposed via the environment or for marine food chain exposure for any life cycle stage.

Limited monitoring data are available for cresyl diphenyl phosphate and these cannot be related to specific activities.

The potential risks identified could be reassessed after additional work, in particular:

- Collation of further site and industry-specific information on releases of cresyl diphenyl phosphate from use in the different types of plastic materials indicated. In particular this relates to use in PVC and in polyurethanes. This work could include:
  - Improved description of practices at sites using cresyl diphenyl phosphate, to determine the realism of the emission estimates, ideally through surveys of representative sites.
  - Targeted monitoring to confirm or replace the calculated PEC values (especially in water, sediment and WWTP sludge). Further environmental monitoring for cresyl diphenyl phosphate is taking place in England and Wales, at one WWTP per Environment Agency region, in both final effluent and associated receiving waters (6 samples at 4 week intervals). The sites are different from those used in the previous monitoring exercise. Sampling is expected to take place from September 2008 until March 2009.

    - Information on the fate of sludges from sites using the substance.
    - Surveys to locate user sites, especially in relation to marine discharges. This is particularly relevant for use in textiles coatings, thermosets and thermoplastics, as these indicate risks only through marine emissions.
- Long-term sediment and soil organism testing and a long-term fish test.
- Studies on the fate of the substance in WWTP (municipal and industrial).
- Clarification of some aspects of the mammalian toxicity data (see Appendix 1).

There may be opportunities to read across information and test results from this substance to the other aryl phosphates assessed in this group (and vice versa). Therefore the additional work indicated above should be considered in relation to that proposed for other members of the group. The overview document should be consulted for more information on this.

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8 Glossary of terms

Term	Description
Biochemical oxygen demand (BOD)	A measure of degradation potential
Bioconcentration factor (BCF)	A measure of chemical uptake, being the ratio between the concentration in an organism and the concentration in an environmental compartment (usually water)
CAS number (no.)	An identifying code number assigned to chemicals by the Chemical Abstract Services. The CAS number is a generally recognised identification reference for a chemical; a substance can have more than one such number
Inherently biodegradable	Some potential for environmental degradation to carbon dioxide and water, and so on, as measured by laboratory screening tests involving microorganisms
Lowest observed effect concentration (LOEC)	The lowest concentration in a toxicity test that gives rise to adverse effects (relative to a control)
Median effective concentration (EC_{50})	The concentration in a toxicity test at which a particular effect is observed in half of the organisms exposed for a specified time
Median lethal loading (LL_{50})	The loading of substance in a water-accommodated fraction that leads to death in half of the organisms exposed for a specified time
Median lethal concentration/dose (LC/D_{50})	The concentration in a toxicity test that can be expected to cause death in half of the organisms exposed for a specified time
No observed effect concentration (NOEC)	The highest concentration in a toxicity test that does not give rise to adverse effects (relative to a control)
Octanol-water partition coefficient (K_{ow})	This parameter gives an indication of the partitioning behaviour of a substance between water and lipid-containing materials such as cell membranes or organic matter in soils and sediments
Readily biodegradable	Rapid environmental degradation to carbon dioxide and water, and so on, as measured by laboratory screening tests involving microorganisms

9 List of abbreviations

Acronym	Description
ABS	Acrylonitrile-styrene butadiene
B	Bioaccumulative
BCF	Bioconcentration factor
BMF	Biomagnification factor
BOD	Biochemical oxygen demand
bw	Bodyweight
CAS	Chemical Abstract Services
CDP	Cresyl diphenyl phosphate
CMR	Carcinogenic, mutagenic and toxic to reproduction
DEHP	Di(2-ethylhexyl)phthalate
DSC	Differential scanning calorimetry
DIN	Deutsche Industrie Norm (German norm)
EC	European Communities
EC_{50}	Median effect concentration
EC_x	As EC_{50}, but for x% effect; x usually being 0, 10, or 100
ECB	European Chemicals Bureau
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances – this lists all chemical substances that were supplied to the market prior to 18th September 1981
EPA	Environmental Protection Agency (USA)
ESD	Emission Scenario Document
ESR	The Existing Substances Regulation – Council Regulation (EEC) 793/93 on the evaluation and control of the risks of 'existing' substances.
EU	European Union
EUSES	European Union System for the Evaluation of Substances (software tool in support of the TGD on risk assessment)
GOT	Glutamyl oxaloaceic transaminase
GPT	Glutamyl pyruvic transaminase
HPLC	High performance liquid chromatography
HPV	High Production Volume (supply above 1,000 tonnes per year)
IUCLID	International Uniform Chemical Information Database: contains non-validated tonnage, use pattern, property and hazard information for chemicals, submitted by industry under the Existing Substances Regulation (ESR)
K_{oc}	Organic carbon normalised distribution coefficient

K_{ow}	Octanol-water partition coefficient
Kp	Solids-water partition coefficient
$L(E)C_{50}$	Median lethal (effect) concentration
LD_{50}	Median lethal dose
LL_{50}	Median lethal loading
log K_{ow}	Log of the octanol-water partition coefficient (K_{ow})
NO(A)EL	No observed (adverse) effect level
NOEC	No observed effect concentration
n.t.p.	Normal temperature and pressure
OECD	Organisation for Economic Cooperation and Development
P	Persistent
PBT	Persistent, bioaccumulative and toxic
PEC	Predicted environmental concentration
pH	Logarithm (to the base 10) of the hydrogen ion concentration [H+]
pK_a	Logarithm (to the base 10) of the acid dissociation constant
PNEC	Predicted no effect concentration
PVC	Polyvinyl chloride
SCAS	Semi-continuous activated sludge unit
SIDS	Screening Information Data Set, OECD
TGA	Thermogravimetric analysis
TGD	Technical Guidance Document
USEPA	Environmental Protection Agency, USA
vB	Very bioaccumulative
vP	Very persistent
vPvB	Very persistent and very bioaccumulative
wt	Weight
wwt	Wet weight
WWTP	Wastewater treatment plant

10 Data collection and peer review process

This report has been produced using publicly available data gathered and assessed by the contractor for the Environment Agency. Additional information has been submitted voluntarily by member companies of the Phosphate Ester Flame Retardant Consortium (PEFRC, http://www.pefrcnet.org/), and the Environment Agency would like to thank them for their cooperation.

The Environment Agency has been keen to ensure that the data used in this report are as complete and accurate as possible. Original reports and literature articles for key studies were retrieved and assessed for reliability wherever possible (it is clearly indicated where this was not the case).

The main scientific literature search was performed in 2002, with some further limited searching to consider specific issues up to 2007.

Drafts of this report have been circulated to key stakeholders in UK and European Industry for comment on several occasions, as well as members of the UK and European chemical regulatory community in July 2007. The Advisory Committee on Hazardous Substances has also provided helpful comments as part of its own deliberations on this substance group (their last review was in September 2007).

In addition, certain technical aspects of the report were peer-reviewed by an independent expert group set up by the Environment Agency for this purpose in April 2007. The experts were:

- Dr Kay Fox (independent consultant);
- Dr Tamara Galloway (University of Plymouth).

Their comments have not been published but are available on request. All comments received have been addressed in the final report where appropriate.

The Institute for Environment and Health wrote the human health effects assessment, and this was peer-reviewed by colleagues at the Health and Safety Executive and Health Protection Agency.

Appendix 1 Points for clarification on mammalian toxicity data

The following points summarise uncertainties in the mammalian dataset (Section 4.4), and may lead to revision of the assessment of human exposure via the environment, and of the classification, if addressed.

- Information on the isomeric composition of the substance tested in the various studies considered in the assessment is limited, reflecting the state of secondary sources from which study data were drawn. It would be useful to have more information on the composition of the test substances used in the studies.
- For the Pharmaco LSR study (1995, cited in BG Chemie 2000) reported in Section 4.4.6, the results of statistical analysis of the effects on protein concentrations (elevated globulins and lowered albumin) reported for the 62.5 mg/kg group (and if values fell within background control ranges) would be helpful, to confirm whether the differences can be discounted in terms of their toxicological significance.
- Xn R48 should be assigned when there is severe organ toxicity below 150 mg/kg/day in a 28-day study or below 50 mg/kg/day in a 90-day study. In the case of this substance, it is difficult to judge whether relevant effects below these cut-offs are of sufficient severity to justify Xn R48, because only a brief description of the findings (notably the liver and kidney histopathological changes) in the key study (MHW 1993) are available. Provision of such data would be necessary to clarify this point.

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