SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

p-cresol

EC No 203-398-6

CAS No 106-44-5

Evaluating Member State(s): United Kingdom

Dated: March 2016

Template Version 2.1
March 2015

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2015

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

p-cresol was originally selected for substance evaluation in order to clarify concerns about:

- CMR (carcinogenicity)
- Suspected endocrine disruptor
- the approach taken for the exposure assessment

During the evaluation no additional concerns were identified.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Under REACH a compliance check was closed after a dossier update.

The eMSCA is aware of the following previous assessments of the human health effects of *p*-cresol:

- National Institute for Occupational Safety and Health (NIOSH), 1978 (cresol, all isomers);
- WHO: International Programme on Chemical Safety Environmental Health Criteria 168 (1995) (cresol, all isomers) (WHO, 1995);
- Dutch Expert Committee for Occupational Standards (DECOS, 1998) (cresol, all isomers);
- SCOEL (2002) (cresol, all isomers) (European Commission, 2002);
- OECD High Production Volume Screening Information Dataset (SIDS) programme (2003)[2] (*m/p*-cresol);
- Cosmetic Ingredient Review (CIR) Expert Panel, 2006, mixed and individual isomers;
- US Department of Health and Human Services, Agency for Toxic Substance and Disease Registry (2008)[3] (cresol, all isomers).

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in Table 1 below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION	
Conclusions	**Tick box**

[2] http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=ad6a5e93-ead2-41df-a046-2f5b64c00f89 (accessed November 2015)

[3] http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=946&tid=196 (accessed November 2015)

Need for follow-up regulatory action at EU level	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	✓

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

4.1.1. Harmonised Classification and Labelling

Not applicable

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Not applicable

4.1.3. Restriction

Not applicable

4.1.4. Other EU-wide regulatory risk management measures

Not applicable

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

REASON FOR REMOVED CONCERN The concern could be removed because	Tick box
Clarification of hazard properties/exposure	✓
Actions by the registrants to ensure safety, as reflected in the registration dossiers (e.g. change in supported uses, applied risk management measures, etc.)	

The hazard assessment of *p*-cresol was targeted to human health (carcinogenicity and, because of its use in consumer products, endocrine disruption). In addition, the approach taken for the human exposure assessment was examined, because it was not clear to the eMSCA how the exposure values used for the risk characterisation were derived in all cases.

Evaluation of the available information indicates that p-cresol does not present a carcinogenic hazard to humans, nor does the good-sized database of repeated-dose toxicity, reproduction and carcinogenicity studies indicate that the substance meets the WHO definition of an endocrine disruptor for human health. Since the substance was placed on the CoRAP in 2012, further information has been provided about exposure to *p*-cresol during its manufacture and use, and the exposure assessment has been updated and refined. This additional information shows that the concentration of *p*-cresol in air during manufacture and use is low and there are few opportunities for workers to come into direct contact with the substance itself or in formulations during processing of these formulations. Further information to support these conclusions can be found in section B of this report.

It is therefore concluded that the concerns listed on the CoRAP have been clarified and no further information is required. No additional concerns were identified during the evaluation.

5.2. Other actions

Not applicable

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

No applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

p-cresol was originally selected for substance evaluation in order to clarify concerns about:

- CMR (carcinogenicity)

- Suspected endocrine disruptor – human health

- the approach taken for the exposure assessment

During the evaluation no additional concerns were identified.

Table 2 shows a list of evaluated endpoints with corresponding outcomes. More details can be found in the relevant sections below.

Table 2

EVALUATED ENDPOINTS Endpoint evaluated	Outcome/conclusion
Mutagenicity, carcinogenicity, repeated-dose toxicity	Carcinogenicity concerns clarified
Reproductive toxicity, repeated-dose toxicity, carcinogenicity	ED concerns for human health not substantiated; no further action
Exposure (human health)	The approach taken for the exposure assessment has been clarified. No concerns have been identified about the suitability of the risk management measures identified in the CSRs.

7.2. Procedure

The evaluation was targeted to the human health hazard concerns outlined above. No evaluation of the environmental fate, hazard or risk assessment was undertaken.

On the basis of an opinion of the ECHA Member State Committee and because of initial grounds for concern relating to carcinogenicity, endocrine disruption potential (human health) and the human health exposure assessment, *p*-cresol CAS No 106-44-5 (EC No 203-398-6) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2015. The updated CoRAP was published on the ECHA website on 17 March 2015. The Competent Authority of the United Kingdom (hereafter called the evaluating MSCA / eMSCA) was appointed to carry out the evaluation.

The initial assessment was initiated on 17 March 2015.

Analytical information provided in the dossiers was assessed to confirm substance identity and composition.

The information included in the evaluation was that in the registration dossiers, publically available information (see references in section 7.14) and information provided to the eMSCA by the registrants.

The draft evaluation report (aspects related to endocrine disruption) was discussed at the 6th meeting of the ED expert group (October 2015).

The eMSCA met with the registrants on 2 November 2015 to discuss the evaluation process and interim conclusions. On 12 February 2016, the eMSCA held a teleconference with the registrants to confirm that the information on exposure and use being presented in the evaluation report was factually correct and that no confidential exposure and use information had been included in the non-confidetial sections of the report.

7.3. Identity of the substance

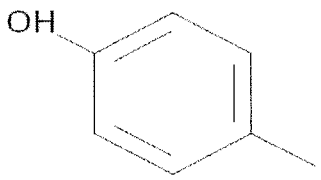
Table 3 displays the identity of the substance according to the ECHA dissemination website.

Table 3

SUBSTANCE IDENTITY	
Public name:	*p*-cresol
EC number:	203-398-6
CAS number:	106-44-5
Index number in Annex VI of the CLP Regulation:	604-004-00-9
Molecular formula:	C_7H_8O
Molecular weight range:	108.14
Synonyms:	4-Methylphenol

Type of substance ☒Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



Generally the information provided by the registrants was sufficient to confirm the identity of the registered substance. However, it is recommended that registrants consider the requirements of Annex VI 2.3.5 to ensure that they are compliant and have data specific to their registration. Further detail on the analysis is provided in the confidential annex.

Each registrant provided some analytical information to support the composition reported in section 1.2 of their dossiers, but registrants are reminded that they should include sufficient information for the analysis to be reproduced. Table 4 gives the typical non-confidential composition, further detail is given in the confidential annex.

Table 4

Constituent			
Constituents	**Typical concentration**	**Concentration range**	**Remarks**
p-cresol	>80% (w/w)		See confidential annex for more details

No validation information such as recovery rates, limit of detection or quantitation were given for any method although one report included analysis of standards of p-cresol and expected impurities.

Some of the analytical reports identified small amounts of impurities (<1%) which were not reported in section 1.2. Registrants are reminded to check their dossiers to ensure compositional information reported in IUCLID (Section 1.2) is correct and supported by the analytical information provided (IUCLID section 1.4). Further detail on the specific analyses and compositions is given in the confidential annex.

For detail on any impurities and additives present see confidential annex.

7.4. Physico-chemical properties

Table 5 lists the physicochemical properties for *p*-cresol from the ECHA dissemination website. All of the information is taken from published articles or handbooks.

Table 5

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Colourless to yellow/brown crystalline solid, with a phenolic odour. Note: Technical product contains impurites so is usually liquid at RT. Crystallisation may occur at colder ambient temperatures while stored. In these cases, the substance is warmed up in order to get a melt. Thus, the substance is mainly used in a liquid form.
Melting/freezing point	35.5°C * see above
Boiling point	202°C
Vapour pressure	14.7 hPa at 25 °C
Water solubility	21.5 g/L at 25°C
Partition coefficient n-octanol/water (Log Kow)	1.94 (pH and temperature not specified)
Flammability	Non flammable – Waiving statement
Flash Point	86°C
Explosive properties	Non-explosive – waiving statement
Oxidising properties	Non oxidising – waiving statement
Granulometry	Not applicable – used in liquid form

Stability in organic solvents and identity of relevant degradation products	idem
Dissociation constant	pKa = 10.26 at 25°C
Relative density	1.034 at 20°C

7.5. Manufacture and uses

7.5.1. Quantities

Table 6

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 - 10 t	☐ 10 - 100 t	☐ 100 - 1000 t	☐ 1000- 10,000 t	☒10,000-50,000 t
☐ 50,000 - 100,000 t	☐ 100,000 - 500,000 t	☐ 500,000 - 1000,000 t	☐ > 1000,000 t	☐ Confidential

More detail is given in the confidential annex.

7.5.2. Overview of uses

The *p*-cresol that is supplied to the EU market may be chemically synthesised or isolated from coal tar/crude oil by fractional distillation and thermal cracking of naptha fractions. In both processes, *p*-cresol is not produced as the substance itself, but as a mixture with m-cresol and other substances depending on the production process. It may be supplied to the market as a mixture of *m*- and *p*-cresol, or further purification processes may be carried out to produce *p*-cresol.

Table 7 indicates the uses listed on ECHA's dissemination site.

Table 7: Disseminated uses for *p*-cresol

USES	Use(s)
Uses as intermediate	Use as an intermediate in chemical synthesis
Formulation	Formulation into mixtures
Uses at industrial sites	Use as a monomer in polymer production Use in processing of liquid and solid polymers Use as a solvent in electric wire enamelling Use as a solvent in the pharmaceutical industry* Laboratory use
Uses by professional workers	Article service life
Consumer Uses	Article service life
Article service life	Electrical batteries and accumulators Plastic articles

* although this use is listed in the information ECHA disseminates from registrations, the registrants indicate that this use only applies to m-cresol. It has therefore not been considered further in this evaluation.

The majority of the tonnage of *p*-cresol manufactured or imported into the EU is used as an intermediate to produce antioxidants, fragrances, flavourings and dyes. Mixtures of m- and p-cresol are also used as intermediates to produce phosphate esters which are used as flame retardant plasticisers, fire-resistant hydraulic fluids, lubricant additives and air filter oils.

Cresols including *p*-cresol are one of the phenolics that can be used to make phenol formaldehyde resins. These include prepolymers known as novolacs which are supplied in photoresist formulations to be used in the manufacture of printed circuit boards and resoles which are thermosetting resins used to manufacture a variety of moulded plastic products. Bakelite is an early example of a phenol formaldehyde resin[4].

Phenol formaldehyde resins are manufactured in a wet process using a step growth polycondensation reaction. The ratio of phenolic to formaldehyde determines whether a liquid novolac or solid resole is produced. Novolacs are produced where the fomaldehyde to phenol ratio is less than 1 and resoles are produced where the formaldehyde to phenol ratio is greater than 1 (typically 1.5).

Cresols can also be used to manufacture polymers using a dry process in which *p*-cresol is reacted with e.g. ethylene or propylene oxide by a polyaddition reaction.

Another use for *p*-cresol is as a solvent in "varnish" formulations which are supplied for wire enamelling. Enamelled wires are used mainly as magnetic wires in windings and coils for use in a variety of electronic articles, in coaxial cables and high voltage transmission cables (UBA, 2002). There are several possible solvents that may be used depending on the polymer and the intended use for the enamelled wire. Cresols tend to be preferred where high molecular weight polymers are used to achieve high temperature resistant coatings.

p-Cresol (FL04.028, JECFA No. 693) is listed in table 1 of regulation 872/2012 as a substance approved for use in the EU for all categories of flavoured food[5,6]. A search of COSING indicates that *p*-cresol is also currently permitted for use in cosmetics as an antimicrobial and perfuming agent[7]. A website from the United States of America (USA) suggests cresols may be used in bath, skin, personal care and hair products, hair dyes and mouthwashes[8]. According to REACH article 2(5), use as a flavouring is not subject to duties to register or covered by the substance evaluation provisions and article 14(5) indicates that it is not necessary to cover risks to human health from use in cosmetic products in the chemical safety report (CSR). These applications will therefore not be considered further in this evaluation. However, they are potential additional sources of human exposure to *p*-cresol.

Historically cresols have been used in wood preservative preparations. However, *p*-cresol was not identified in the 2000s as an existing active ingredient in the Biocidal Products Directive (BPD), and neither has it been supported for assessment under the EU Biocides Regulation (EU BPR) which replaced it. Therefore, there should be no biocidal product on the EU market with *p*-cresol present as an active ingredient. There is no information to suggest that it is used as a co-formulant in non-agricultural pesticides covered by the Control of Pesticides Regulations (COPR) in UK.

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[4] https://en.wikipedia.org/wiki/Phenol_formaldehyde_resin

[5] https://webgate.ec.europa.eu/sanco_foods/main/?event=substance.view&identifier=284

[6] http://apps.who.int/food-additives-contaminants-jecfa-database/chemical.aspx?chemID=693

[7] http://ec.europa.eu/growth/tools-databases/cosing/index.cfm?fuseaction=search.details_v2&id=35872

[8] http://www.cosmeticsinfo.org/ingredient/cresols-and-isopropyl-cresols

In addition to these intentional uses, there are several additional background sources of exposure to *p*-cresol. These will be covered in more detail in section 7.12.

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 8

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
604-004-00-9	p-cresol	203-398-6	106-44-5	Acute Tox. 3 * Acute Tox. 3 * Skin Corr. 1B	H301 H311 H314		Note C

7.6.2. Self-classification

- In the registration(s):

Some registrants apply the additional classification:

Aquatic Chronic 3 – H412

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory:

Eye Dam. 1 – H318
STOT SE 3 – H335 (RTI)
STOT SE1 – H370 (kidney, central nervous system)
Aquatic Chronic 3 – H412

7.7. Environmental fate properties

Not evaluated

7.8. Environmental hazard assessment

Not evaluated

7.9. Human Health hazard assessment

Carcinogenicity and endocrine disruption were the initial concerns for *p*-cresol. Therefore, the following endpoints were evaluated in detail: mutagenicity, carcinogenicity, reproductive toxicity and repeated-dose toxicity. The other human health endpoints were briefly evaluated to identify additional potential concerns.

The registered substance is *p*-cresol. Some of the studies provided in the registration dossier were conducted with a mixture of *m-/p*-cresol (a 60:40 ratio). Where studies are available on both *p*-cresol and the *m-/p*-cresol mixture, the findings and NOAELs have been compared to verify that it is appropriate to apply findings from the mixture to the single p-isomer for the end-points for which only data on the mixture is available.

The study reliabilities given in the tables have been assigned by the eMSCA.

The eMSCA is aware of the following previous assessments of the human health effects of *p*-cresol:

- National Institute for Occupational Safety and Health (NIOSH), 1978 (cresol, all isomers);
- WHO: International Programme on Chemical Safety Environmental Health Criteria 168 (1995) (cresol, all isomers) (WHO, 1995);
- Dutch Expert Committee for Occupational Standards (DECOS, 1998) (cresol, all isomers);
- SCOEL (2002) (cresol, all isomers) (European Commission, 2002);
- OECD High Production Volume Screening Information Dataset (SIDS) programme (2003)[9] (*m/p*-cresol);
- Cosmetic Ingredient Review (CIR) Expert Panel, 2006, mixed and individual isomers;
- US Department of Health and Human Services, Agency for Toxic Substance and Disease Registry (2008)[10] (cresol, all isomers).

SCOEL concluded that a NOAEL for rats of 50 mg/kg/d for the cresol isomers was appropriate from the oral animal data. As local irritation is the critical effect of cresol vapours and no adequate inhalation studies were available, SCOEL did not make a recommendation on an occupational exposure limit. A 'skin' notation was recommended because dermal absorption could make a substantial contribution to the total body burden.

7.9.1. Toxicokinetics

The available information on the toxicokinetics of *p*-cresol has not been evaluated by the eMSCA but is briefly summarised below to help inform on the evaluated end-points.

Oral uptake in rabbits following a single gavage dose was >75% (IUCLID dossier; DECOS, 1998). It has been suggested that cresol administered by oral gavage diffuses directly through the gastric and small intestinal walls (Morinaga *et al.*, 2004). *In vitro* percutaneous penetration through hairless mouse stratum corneum was 77% by 24 hours. No information is available on the absorption of *p*-cresol after inhalation exposure, but based on the oral absorption it is assumed to be high.

One study in rats showed that after oral gavage administration of an *m-/p*-cresol mixture, unconjugated and conjugated *p*-cresol was distributed to the blood, brain, kidney, liver, lung, muscle and spleen (Morinaga *et al.*, 2004). In a rabbit study, the major metabolic pathway for the isomers was conjugation with glucuronic acid and inorganic sulphate; excretion in urine as free and conjugated p-hydroxybenzoic acid was also detected. *p*-Cresol is also metabolised to a reactive quinone-methide intermediate (DECOS, 1998). The NTP reports that humans exposed orally to wood creosote excreted *p*-cresol in urine primarily as a glucuronide conjugate, a sulphate conjugate and as the free cresol; the characterisation of three additional glutathione conjugates in human microsomes incubated with *p*-cresol indicated the presence of a bioactivation pathway that involved the formation of the reactive intermediate 4-methyl-1,2-benzoquinine NTP, 2008. *p*-Cresol is a by-product of protein breakdown, being one of the metabolites of the amino acids tyrosine and phenylalanine. It is also produced by anaerobic gut microflora from the degradation of amino acids and thus may naturally be found in faeces. The one available animal study, in rabbits, indicates, however, that the main excretion route for orally-administered cresols is urinary.

[9] http://webnet.oecd.org/hpv/ui/SIDS_Details.aspx?id=ad6a5e93-ead2-41df-a046-2f5b64c00f89 (accessed November 2015)

[10] http://www.atsdr.cdc.gov/ToxProfiles/TP.asp?id=946&tid=196 (accessed November 2015)

7.9.2. Acute toxicity and Corrosion/Irritation

p-Cresol has a harmonised classification on Annex VI of Regulation (EC) 1272/2008 for acute oral toxicity category 3 (H301), acute dermal toxicity category 3 (H311) and skin corrosion category 1B (H314).

7.9.3. Sensitisation

The registrants concluded the substance is not a sensitiser; based on the information in the registration dossier, the eMSCA can support this conclusion.

7.9.4. Repeated dose toxicity

As repeated-dose toxicity informs on the concerns for carcinogenicity and endocrine disruption, this end-point has been evaluated in full.

7.9.4.1. Oral

The registration dossier contains information from a number of oral repeated-dose studies in rats and mice on *p*-cresol and a mixture of *m*-/*p*-cresol. The eMSCA has also identified additional repeated-dose studies with the *m*-/*p*-cresol mixture.

7.9.4.1.1. Rats

Table 9. Summary of oral repeated-dose toxicity studies in rats

<table>
<tr><th>Method</th><th>Dose levels</th><th>Results</th></tr>
<tr><td colspan="3">P-CRESOL</td></tr>
<tr><td>Oral (dietary)

28 days

Rats Fischer 344/N 5 / sex / dose

p-cresol (>98% purity)

GLP

Similar to OECD 407

IUCLID 7.5.1; NTP, 1992
Reliability 1
Full study report evaluated</td><td>0, 300, 1000, 3000, 10 000 and 30 000 ppm

Equivalent to

0, 25, 87, 256, 835, 2180 mg/kg/d in males

0, 25, 83, 242, 769, 2060 mg/kg/d in females</td><td>Examinations/observations included clinical signs, body weight, feed consumption, organ weights, gross pathology and histopathology.

No deaths at any dose level.

Hunched posture, rough hair coat and thin appearance during the first week at 30 000 ppm. No clinical signs reported at lower doses.

The findings of note on body and organ weight are reported in the table below
<table>
<tr><th>ppm</th><th>0</th><th>300</th><th>1000</th><th>3000</th><th>10 000</th><th>30 000</th></tr>
<tr><td>Males</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean terminal body weight</td><td>100%</td><td>102%</td><td>102%</td><td>97%</td><td>96%</td><td>71%**</td></tr>
<tr><td>Mean terminal body weight gain</td><td>100%</td><td>102%</td><td>102%</td><td>95%</td><td>88%</td><td>41%**</td></tr>
<tr><td>Liver relative weight</td><td>100%</td><td>104%</td><td>102%</td><td>105%</td><td>115%**</td><td>124%**</td></tr>
<tr><td>Kidney weight
relative

absolute</td><td>100%

100%</td><td>95%

97%</td><td>96%

98%</td><td>104%

101%</td><td>112%*

108%</td><td>122%**

85%</td></tr>
<tr><td>Brain relative change</td><td>100%</td><td>98%</td><td>97%</td><td>100%</td><td>105%</td><td>134%</td></tr>
</table>
</td></tr>
</table>

Right testes relative weight	100%	98%	96%	102%	106%	121% *
Females						
Mean terminal body weight	100%	106%	107%	107%	96%	84%
Mean terminal body weight gain	100%	109%	121%	111%	91%	54%
Liver relative weight	100%	-99%	98%	108% *	112% *	124% *
Kidney weight relative absolute	100% 100%	98% 104%	106% 100%	100% 107%	104% 100%	110% * 93%
Brain relative weight	100%	100%	100%	100%	104%	116%

No gross lesions recorded at necropsy.

The findings of note at histopathology are summarised below.

Dose (ppm)	**0**	**300**	**1000**	**3000**	**10 000**	**30 000**
Males: incidence (severity)						
Bone marrow hypocellularity	0/5	-	0/5	1/5 (2.0)	1/5 (2.0)	5/5 (3.0)
Nasal Olfactory epithelium atrophy	0/5	-	0/5	0/5	0/5	5/5 (2.0)
Respiratory epithelium – hyperplasia	0/5	-	0/5	1/5 (1.0)	4/5 (2.7)	5/5 (2.8)
- squamous metaplasia	0/5	-	0/5	0/5	0/5	2/5 (2.0)
Females: incidence (severity)						
Bone marrow hypocellularity	0/5	-	-	0/5	1/5 (2.0)	3/5 (2.7)
Nasal Olfactory epithelium atrophy	0/5	-	0/5	1/5 (1.0)	0/5	4/5 (1.7)
Respiratory epithelium – hyperplasia	0/5	-	0/5	1/5 (1.0)	3/5 (3.0)	3/5 (2.3)
- squamous metaplasia	0/5	0/1	0/1	0/5	1/5 mild	0/5
Uterus-atrophy of endometrium	0/5	0/1	0/1	0/1	0/5	3/5 (2.7)

Severity scores: 1 = minimal, 2 = mild, 3= moderate, 4 = severe

No histopathological findings in the kidneys, liver or testes were reported.

<table>
<tr><td></td><td></td><td>NOAEL = 3000 ppm (256 mg/kg/d in males and 242 mg/kg/d in females) based on > 10% increase in liver weight and mild to moderate hyperplasia of the nasal respiratory epithelium at 10 000 ppm.</td></tr>
<tr><td>Oral (gavage)

90 days with interim kill at week 7

Rats, Sprague Dawley, 30 rats/sex/dose

An additional 10 rats / sex selected for baseline haematology & clinical chemistry (no treatment)

p-cresol (99.9% purity)

OECD Guideline 408, GLP

Reliability 1 IUCLID 7.5.1; Dietz & Mulligan, 1988

Full study report evaluated.</td><td>0, 50, 175, 600 mg/kg/d in corn oil</td><td>Examinations / observations: clinical signs, ophthamology, haematology, clinical chemistry, urinanalysis, gross and histopathology.

At 600 mg/kg/d, 3/30 females died within the first 3 days; two of these demonstrated tremors, convulsions and coma prior to death. Other overt signs of toxicity in most of the surviving animals at this dose included lethargy, excessive salivation, tremors, convulsions and coma.

There were no deaths or overt clinical signs of toxicity at lower doses.

Effects on body weight, body weight gain and organ weights are summarised below.
<table>
<tr><th>mg/kg bw/d</th><th>0</th><th>50</th><th>175</th><th>600</th></tr>
<tr><td>Males</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean terminal body weight</td><td>100%</td><td>97%</td><td>94%</td><td>86%*</td></tr>
<tr><td>Mean terminal body weight gain</td><td>100%</td><td>95%</td><td>93%</td><td>79%*</td></tr>
<tr><td>Left kidney relative weight</td><td>100%</td><td>106%</td><td>109%*</td><td>116%*</td></tr>
<tr><td>Right kidney relative weight</td><td>100%</td><td>106%</td><td>117%*</td><td>116%*</td></tr>
<tr><td>Right testes relative weight</td><td>100%</td><td>108%</td><td>107%</td><td>117%*</td></tr>
<tr><td>Left testes relative weight</td><td>100%</td><td>107%</td><td>104%</td><td>116%*</td></tr>
<tr><td>Heart relative weight</td><td>100%</td><td>99%</td><td>104%</td><td>110%*</td></tr>
<tr><td>Females</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Mean terminal body weight</td><td>100%</td><td>96%</td><td>98%</td><td>92%*</td></tr>
<tr><td>Mean terminal body weight gain</td><td>100%</td><td>99%</td><td>100%</td><td>87%*</td></tr>
<tr><td>Right kidney relative weight</td><td>100%</td><td>106%</td><td>103%</td><td>111%*</td></tr>
<tr><td>Heart relative weight</td><td>100%</td><td>102%</td><td>97%</td><td>104%</td></tr>
</table>
Alterations in haematology were observed at ≥ 175 mg/kg bw/d in females only: reductions in red blood cell count, haemoglobin concentration & haematocrit. Physiological compensatory responses to the mild anaemic state (reticulocytes, macrocytosis, elevated numbers of RBC) were not evident.

Changed clinical chemistry parameters comprised statistically significant elevations in alanine aminotransferase (ALT) (high-dose females, interim & terminal sacrifices) and aspartate aminotransferase (AST) (high-dose females); attributed to unusually high values in 4 animals. Serum cholesterol was statistically significantly increased in high-dose females (terminal sacrifice only), as was protein in mid- and high-dose males.</td></tr>
</table>

<table>
<tr><td></td><td></td><td>No findings at gross necropsy.

The histopathology findings are summarised below:

<table>
<tr><th>mg/kg bw/d</th><th>0</th><th>50</th><th>175</th><th>600</th></tr>
<tr><td>Males</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Nephropathy- (incidence/total)
severity</td><td>4/20

3 minimal
1 mild</td><td>11/20*

9 minimal
2 mild</td><td>7/20

7 minimal</td><td>12/20*

9 minimal
3 mild</td></tr>
<tr><td>Trachea – epithelial metaplasia</td><td>0/20</td><td>0/20</td><td>1/20</td><td>10/20*</td></tr>
<tr><td>Females</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Trachea – epithelial metaplasia</td><td>0/20</td><td>1/20</td><td>1/20</td><td>9/19*</td></tr>
</table>

Nephropathy was not reported in females. No adverse findings in the ovaries, uterus or testes were reported.

NOAEL= 50 mg/kg bw/d based on statistically significant increase in relative kidney weight in males at 175 mg/kg/d.</td></tr>
<tr><td>Oral gavage in corn oil

90-day neurotoxicity study

Rats, CD, 10/sex/ dose group, 20/ sex as controls

p-cresol (purity not stated)

IUCLID 7.9 & additional summary provided by registrants. Reliability 4

Non-guideline and no data on GLP</td><td>0, 50, 175, 600 mg/kg/d</td><td>Examinations / observations: body weight gain, food consumption, clinical signs and neurobehavioural signs

Deaths occurred in 1, 0, 0, and 8 animals (4 males, 4 females) at 0, 50, 175 & 600 mg/kg/d. Deaths occurred throughout the study but with highest incidence during the first few weeks. The deaths were reported to be the direct effect of the substance (2 males at 600 mg/kg/d), aspiration or inhalation of the substance (2 males, 3 females at 600 mg/kg/d) or pulmonary oedema (1 female at 600 mg/kg/d).

Mean body weight of males in the 600 mg/kg/d group statistically significantly reduced during week 1 only; food consumption of males & females reduced early in the study.

Overt clinical signs were recorded sporadically in all treatment groups and included: salivation, myotonus, tremors, hypoactivity, rapid respiration, myoclonus, low body posture, laboured respiration.

Observations for neurobehavioral signs of toxicity were recorded once during pre-treatment, 1 & 6 hours after dosing on study day 1, & prior to dosing on study days 2, 7, 14, 30, 60 & 90. At 600 mg/kg/d, the incidence of palpebral closure, rales and laboured respiration were greater than controls during the initial part of the study; and locomotor activity was less than that of controls in the high-dose animals (males at day 90, females at 24 hours). No other dose-related adverse effects on neurobehaviour.

Brain weights were unaffected by treatment. Gross and microscopic examination of nervous-sytsem tissues revealed no treatment-related lesions when stained with haematoxylin and eosin.

NOAEL = 175 mg/kg/d based on deaths and changes in neurotoxic test parameters at 600 mg/kg/d.</td></tr>
<tr><td colspan="3">M-/P-CRESOL MIXTURE</td></tr>
<tr><td>Oral</td><td>0, 300,</td><td>Examinations/observations included clinical signs, body weight, feed</td></tr>
</table>

(dietary) 28 days Rats F344/N, 5 / sex / dose *m-/p*-cresol (>98% purity, 60:40 ratio) GLP Similar to OECD 407 NTP, 1992 Reliability 1 Full study report evaluated	1000, 3000, 10000 and 30000 ppm Equivalent to 0, 26, 90, 261, 877, 2600 mg/kg/d in males 0, 27, 95, 268, 886, 2570 mg/kg/d in females	consumption, organ weights, gross pathology and histopathology. There were no deaths in any group. Food intake reduced during first week only, resulting in thin appearance up until but not beyond day 6. Other overt clinical signs of toxicity not reported. Changes in body weight, body weight gain and organ weights are summarised below.

ppm	**0**	**300**	**1000**	**3000**	**10 000**	**30 000**
Males						
Mean terminal body weight	100%	104%	97%	96%	96%	82%*
Mean terminal body weight gain	100%	100%	100%	98%	95%	67%*
Liver relative weight	100%	105%	105%	108% *	120% *	132% *
Kidney weight relative absolute	100% 100%	98% 98%	104% 101%	103% 100%	111% 107%	130% * 106%
Brain relative weight	100%	101%	103%	103%	104%	119% *
Right testes relative weight	100%	99%	98%	102%	104%	116% *
Females						
Mean terminal body weight	100%	102%	104%	102%	101%	94%
Mean terminal body weight gain	100%	103%	106%	93%	91%	77%
Liver relative weight	100%	104%	107% *	105% *	121% *	133% *
Kidney weight relative absolute	100% 100%	101% 102%	100% 103%	103% 105%	109% * 109% *	117% * 111% *
Brain relative weight	100%	100%	99%	99%	101%	106%

No gross lesions noted at necropsy.

The histopathology findings of note are summarised below.

Dose (ppm)	**0**	**300**	**1000**	**3000**	**10 000**	**30 000**
Males: incidence (severity)						
Bone marrow hypocellularity	0/5	-	-	-	0/5	3/5 (1.0)
Nasal Respiratory epithelium – hyperplasia	0/5	0/5	0/5	5/5 (2.0)	5/5 (2.4)	5/5 (3.2)

		Oesophagus epithelium- hyperkeratosis: 0/5 - 0/5 3/5 (1.0) 4/5 (1.0) 5/5 (1.2) hyperplasia: 0/5 - 0/5 3/5 (1.0) 4/5 (1.0) 5/5 (1.4) Forestomach epithelium hyperplasia: 0/5 - - 0/5 2/5 (1.0) 5/5 (1.4) Thyroid increased colloid in follicular cell: 0/5 - 0/5 3/5 (1.0) 5/5 (1.0) 5/5 (1.8) *Females: incidence (severity)* Bone marrow hypocellularity: 0/5 - - 0/5 1/5 (1.0) 5/5 (1.2) Nasal Respiratory epithelium – hyperplasia: 0/5 0/5 3/4 (1.0) 5/5 (1.0) 5/5 (1.6) 5/5 (1.0) Oesophagus epithelium- hyperkeratosis: 0/5 - - 0/5 2/5 (1.0) 5/5 (1.2) hyperplasia: 0/5 - - 0/5 2/5 (1.0) 5/5 (1.0) Forestomach epithelium hyperplasia: 0/5 - - 0/5 2/5 (1.0) 5/5 (1.0) hyperkeratosis: 0/5 - - 0/5 2/5 (1.0) 5/5 (1.2) Thyroid: increased colloid in follicular cell: 1/5 (1.0) - 0/5 4/5 (1.0) 5/5 (1.8) 4/5 (3.2) Severity scores: 1 = minimal, 2 = mild, 3= moderate, 4 = severe No histopathological findings in the kidneys, uterus or testes were reported. NOAEL = 1000 ppm (equivalent to 90 / 95 mg/kg/d in males and females, respectively) based on increased incidences of histopathology findings at ≥ 3000 ppm (oesophagus, nasal tissues, thyroid gland).
Oral (dietary) 90 days Rats, F344N, 20/sex/dose *m-/p*-cresol 60:40 mixture (>98% purity) GLP Similar to	0, 1880, 3750, 7500, 15 000, 30 000 ppm Equivalent to Males: 0, 123, 241, 486, 991, 2014 mg/kg/d Females: 0, 131, 254, 509, 1024, 2050 mg/kg/d	10/sex/dose were examined for clinical chemistry, haematology and urinalysis. 10/sex/dose were examined for reproductive toxicity, gross pathology, organ weights, clinical pathology and histopathology. There were no deaths in any dose group. Clinical signs of toxicity at 30 000 ppm included rough hair coat (males & females) and thin appearance (females). Urine-stained fur was recorded in high-dose males and mid- & high-dose females. Food consumption was reduced in the high-dose group (males & females) during the first week. Changes in body weight, body weight gain and organ weights are summarised below. **ppm** | **0** | **1880** | **3750** | **7500** | **15000** | **30000** *Males* Mean terminal: 100 96% 101 98% 93%* 83%*

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body weight	%		%			
Mean terminal body weight gain	100 %	95%	103 %	97%	90%	73%*
Right kidney absolute weight % relative weight %	100 % 100 %	100 104	106* 105	107* 107*	118* 117*	125* 125*
Liver relative weight %	100 %	102	104	112*	126*	136*
Right testes relative weight %	100 %	102	100	103	108*	119*
Brain relative weight	100 %	104 %	103 %	103 %	109%	129% *
Females						
Mean terminal body weight	100 %	99%	100 %	97%	95% *	88%*
Mean terminal body weight gain	100 %	98%	101 %	94%	89% *	75%*
Liver relative weight %	100 %	103 %	100 %	108 %	115 %	127%
Right kidney absolute weight relative weight	100 % 100 %	98% 99%	107 % 101 %	101 % 101 %	98% 104 %	87%* 115%*
Brain relative weight	100 %	103 %	99%	100 %	102 %	120%

Haematology & clinical chemistry: there was some evidence of haemoconcentration early in the study at 30 000 ppm but no changes by 90 days. Increased serum alanine aminotransferase & sorbitol dehydrogenase (males at 30 000 ppm) on day 5 only. Total bile acids elevated in males & females from 1880 ppm. Serum levels of 5'-nucleotidase decreased from 7500 ppm.

The histopathology findings of note are summarised below.

Dose (ppm)	**0**	**1880**	**3750**	**7500**	**15 000**	**30 000**
Males: incidence (severity)						
Bone marrow hypocellularity	0/10	0/10	0/10	0/10	1/10 (1.0)	8/10 (1.0)
Nasal Respiratory epithelium – hyperplasia	0/10	3/10 (1.0)	8/10 (1.1)	10/10 (1.4)	8/10 (2.2)	10/10 (3.8)
Glandular hyperplasia	0/10	3/10 (1.0)	8/10 (1.5)	10/10 (1.6)	9/10 (2.6)	9/10 (3.8)
Thyroid gland – increased colloid in follicles	0/10	0/10	0/10	0/10	7/10 (1.1)	9/10 (1.6)
Females: incidence (severity)						
Bone marrow hypocellularity	0/10	0/10	0/10	0/10	0/10	6/10 (1.0)
Nasal Respiratory epithelium –	3/10 (1.0)	1/10 (1.0)	5/10 (1.2)	9/10 (1.7)	8/10 (2.0)	10/10 (2.8)

		hyperplasia Glandular hyperplasia	0/10	2/10 (1.0)	6/10 (1.3)	10/10 (2.1)	8/10 (2.5)	6/10 (2.8)
		Thyroid increased colloid in follicular cell	0/10	0/10	1/10 (1.0)	6/10 (1.2)	7/10 (1.6)	8/10 (1.6)
		Uterus atrophy	0/10	0/10	0/10	0/10	3/10 (1.0)	7/10 (1.7)
		Severity scores: 1 = minimal, 2 = mild, 3= moderate, 4 = severe In males, testes and epididymides weights were unaffected by exposure to *m-/p*-cresol. Sperm parameters were unaffected apart from a very slight (4%) decrease in motility at 30 000 ppm which the study authors considered to be biologically insignificant. In females, a dose-related increase in oestrus cycle length occurred: 4.5, 4.7, 5.1* and 5.1* days in the 0, 1880, 7500 and 30 000 ppm groups, respectively. NOAEL = 1880 (123 mg/kg/d) based on increased absolute kidney weight from 3750 ppm (241 mg/kg/d).						

* Statistically significant, $p \leq 0.05$

p-Cresol has been tested in repeated-dose toxicity studies in rats and gavage at doses of > 2000 mg/kg/d by dietary administration and up to 600 mg/kg/d by gavage administration. There were no deaths at any doses given in the feed but 3/30 females died at 600 mg/kg/d when the substance was given by gavage.

In a well-reported 28-day study, relative increases in liver, kidney, brain and testes weights were reported at 30 000 ppm. The relative liver weight of males and females and relative kidney weight of males was also increased at 10 000 ppm. None of the organ weight changes was associated with any histopathological changes. The increases in relative brain and testes weight, occurring only in the high-dose group, were secondary to the decreased body weight and were not indicative of specific target organ toxicity. Histopathology changes in other organs and tissues included the bone marrow (minimal to mild bone marrow depletion as evidenced by decreased numbers of haematopoietic cells), the nasal cavity (respiratory epithelial hyperplasia and squamous metaplasia and olfactory epithelial atrophy) and mild to moderate uterine atrophy in 3/5 females at 30 000 ppm. The NOAEL for systemic and local effects was 3000 ppm (256 mg/kg/d in males and 242 mg/kg/d in females), based on > 10% increase in liver weight and mild to moderate hyperplasia of the respiratory epithelium at 10 000 ppm.

An additional 28-day dietary study in rats was included in the registration dossier (IUCLID 7.5.1) in which *p*-cresol (purity not stated) was administered in doses up to 500 ppm (equivalent to approximately 45 mg/kg/d). As only limited information was available, only males were included and from the study description it seemed that only the kidneys, livers, adrenals and testes were weighed, this study does not add to the evaluation (not summarised in the table above). No gross lesions were reported; it is not clear if histopathology was conducted.

In a 90-day gavage study with *p*-cresol, 3/30 females at 600 mg/kg/d died within three days of the start of the study. Two of these females and most of the surviving animals in this dose group exhibited signs of central nervous system effects (convulsions, tremors, lethargy, coma). A mild anaemic state was induced but without compensatory physiological mechanisms. The bone marrow also appeared to be normal. Increases in relative brain, liver and heart weight were linked to decreases in body weight at the top dose and were not accompanied by histopathology changes. Histopathology findings were confined to nephropathy in males only, but without a clear dose-response relationship in

incidence and severity, and epithelial metaplasia of the trachea in the high-dose group males and females; the bronchi and lower airways did not exhibit this change. The NOAEL was 50 mg/kg bw/d based on the statistically significant increase in relative kidney weight (without a change in absolute kidney weight) in males and mild anaemia in females at ≥ 175 mg/kg/d.

The neurotoxicity of *p*-cresol has been investigated in a separate 90-day gavage study in rats. There were essentially no treatment-related deficits in general appearance or neuromuscular, sensory or motor functions; however, only a study summary was available to the eMSCA. Notwithstanding, the effects reported in the neurotoxicity investigations (lacrimation, palpebral closure, rales, laboured respiration, hypoactivity in the high-dose group only and generally reported in the earlier stages of the study) do not raise a concern for neurotoxicity. Furthermore, there were no treatment-related effects on neurobehaviour, nor gross or microscopical lesion in the brain or nervous-system tissues. The NOAEL was 175 mg/kg/d, based on treatment-related deaths and changes in some investigated parameters at 600 mg/kg/d.

In a 28-day study with dietary administration of the *m-/p*-cresol mixture, besides decreased body weights and body weight gains, the main adverse effects were on relative kidney and liver weights. Increased relative brain and testes weights in the high-dose males (30 000 ppm) were a reflection of the reduced body weight gain in this group. Histopathology changes were recorded in the respiratory epithelial hyperplasia of the nasal cavity (primarily the anterior section), with the hyperplastic areas being associated with single-cell necrosis. Increased colloid within thyroid follicles was demonstrated by increased follicle diameter and flattening of epithelial cells. Minimal to mild bone marrow hypocellularity was evidenced by the decreaed numbers of haematopoietic cells and corresponding relative increases in adipocytes. At the three highest doses, minimal to mild epithelial hyperplasia and hyperkeratosis of the oesophagus and fore-stomach were noted. The NOAEL for systemic and local effects was 1000 ppm (equivalent to 90 / 95 mg/kg/d in males and females, respectively) based on increased incidences of histopathology findings at ≥ 3000 ppm (local effects on oesophagus and nasal tissues, systemic effect on thyroid gland).

In a 90-day dietary study in rats with a mixture of *m-/p*-cresol, there were statistically significant reductions in final body weights at 15 000 and 30 000 ppm. In common with the other studies, increased relative kidney weights were observed (from 3750 ppm). Although relative testes and brain weights were increased, absolute weights weren't; these findings are considered to be a consequence of the decreased body weight. Some evidence of hepatocellular injury was provided by the transiently elevated serum enzymes, elevated total bile acids and decreased 5'-nucleotidase. The urinalysis results did not provide any evidence of renal injury. An effect that was reported only with the mixture was lengthening of the oestrus cycle. This parameter was not investigated in the 28-day supporting study conducted by the same authors on *p*-cresol alone; however, in an available two-generation study conducted with the pure *p*-isomer in rats there was no effect on oestrus cycle length at doses that resulted in severe parental toxicity (section 7.9.7). The NOAEL was 1880 ppm (equivalent to 123 / 131 mg/kg/d in males and females, respectively) based on increased absolute kidney weight in males from 3750 ppm.

The non-neoplastic findings in the carcinogenicity study are summarised in section 7.9.6.

7.9.4.1.2. Mice

Table 10. Summary of oral repeated-dose toxicity studies in mice

Method	Dose levels	Results
	P-CRESOL	

Oral (dietary) 28 days Mice, B6C3F1, 5/sex/dose *p*-cresol (purity>98%) GLP Similar to OECD 407 Reliability 1 Full study report evaluated IUCLID 7.5.1.; NTP, 1992	0, 300, 1000, 3000, 10 000 ppm (0, 50, 163, 469, 1410 males and 0, 60, 207, 564, 1590 mg/kg bw/d females) 30 000 ppm given but mg/kg bw/d not stated as all animals died	Examinations/observations included clinical signs, body weight, feed consumption, organ weights, gross pathology and histopathology. All animals died at 30 000 ppm or were sacrificed moribund during week 1. One male at 10 000 ppm also died. Clinical signs in decedents and survivors at 30 000 and 10 000ppm (males): hunched posture, rough hair coat, lethargy, hypothermia, laboured breathing and paleness. Feed consumption of females at 10 000 ppm was reduced during the first 2 weeks and the first 5 days for males. Treatment-related effects on body weight, body weight gain and organ weights are summarised below.

ppm	**0**	**300**	**1000**	**3000**	**10 000**
Males					
Terminal body weight	100%	100%	102%	100%	83%*
Terminal body weight gain	100%	100%	97%	97%	8%*
Liver relative weight	100%	98%	107%	108%	115% *
Kidney weight relative absolute	100% 1005	108% 106%	108% 110%	111% * 111%	112% * 92%
Heart relative weight	100%	108%	106%	106%	112% *
Females					
Liver absolute weight	100%	105%	103%	104%	116% *
Liver relative weight	100%	101%	104%	106%	120% *

There were no gross lesions at necropsy.

Histopathology findings are summarised below.

ppm	**0**	**300**	**1000**	**3000**	**10000**	**30000**
Males: incidence (severity)						
Bone marrow hypocellularity	0/5	-	-	-	0/5	5/5 (2.0)
Renal tubule necrosis	0/5	-	-	-	0/5	4/5 (1.7)
Liver centrilobular atrophy centrilobular necrosis liver necrosis	0/5 0/5 0/5	- - -	- - -	- - -	0/5 0/5 0/5	1/5 1/5 2/5
Nasal respiratory epithelium atrophy hyperplasia	0/5 0/5	0/5 0/5	0/5 3/5 (1.0)	0/5 5/5 (1.8)	0/5 5/5 (2.0)	1/5 (2.0) 1/5 (2.0)
Olfactory epithelium atrophy	0/5	0/5	0/5	0/5	0/5	1/5

necrosis	0/5	0/5	0/5	0/5	0/5	(2.0) 2/5 (2.5)
Females: incidence (severity)						
Bone marrow hypocellularity	0/5	-	-	-	0/5	3/5 (2.0)
Renal tubule necrosis	0/5	-	-	-	0/5	3/5 (1.7)
Liver centrilobular necrosis	0/5	-	-	-	0/5	1/5 (2.0)
Nasal respiratory epithelium hyperplasia	0/5	1/5 (1.0)	2/5 (1.0)	4/5 (1.7)	5/5 (1.6)	1/5 (1.0)
Olfactory epithelium necrosis	0/5	0/5	0/5	1/5 min	0/5	3/5 mild

Severity scores: 1 = minimal, 2 = mild, 3= moderate, 4 = severe

NOAEL = 300 ppm (50 mg/kg bw/d in males and 60 mg/kg bw/d in females) based on increased incidences of histopathology findings (nasal respiratory epithelium hyperplasia) at 1000 ppm.

M-/P-CRESOL MIXTURE

Oral (dietary) 28 days Mice, B6C3F1, 5/sex/dose *m-/p*-cresol (purity>98%) GLP Similar to OECD 407 Reliability 1 Full study report evaluated IUCLID 7.5.1.; NTP, 1992	0, 300, 1000, 3000, 10 000, 30 000 ppm Equivalent to Males: 0, 50, 161, 471, 1490, 4530 mg/kg/d Females: 0, 65, 200, 604, 1880, 4730 mg/kg/d	Examinations/observations included clinical signs, body weight, feed consumption, organ weights, gross pathology and histopathology. There were no deaths in any dose group. Overt clinical signs observed at 30 000 ppm: alopecia, dehydration, hunched posture, hypothermia, lethargy, rough hair coat & thin appearance. Feed consumption was decreased in males & females during the first week of the study. Changes in body weight and organ weights are reported below.

ppm	**0**	**300**	**1000**	**3000**	**10000**	**30000**
Males						
Terminal body weight	100%	95%	96%	94%	91%	73%*
Terminal body weight gain	100%	70%*	91%	79%	47%*	Lost weight
Brain relative weight	100%	99%	103%	103%	109%	129%*
Kidney weight absolute relative	100% 100%	92% 97%	96% 101%	98% 104%	98% 107%	76%* 104%
Liver relative weight	100%	98%	108%*	114%*	129%*	140%*
Right testis, relative	100%	107%	102%	102%	105%	121%*
Females						
Terminal body weight	100%	97%	103%	101%	100%	78*
Terminal body weight gain	100%	103%	100%	105%	95%	Lost weight

		Brain relative weight: 100% / 103% / 99% / 100% / 102% / 120% * Kidney weight: 100% / 92% / 99% / 102% / 105% / 85% absolute: 100% / 94% / 97% / 100% / 106% / 109% relative: * Liver relative weight: 100% / 100% / 102% / 110% * / 131% * / 134% * There were no gross necropsy findings. Histopathology findings are summarised below.

ppm	0	300	1000	3000	10000	30000
Males: incidence (severity)						
Bone marrow hypocellularity	0/5	-	-	-	0/5	2/5 (1.5)
Lung bronchiolar hyperplasia	0/5	-	-	-	0/5	5/5 (1.2)
Oesophagus epithelium hyperplasia	0/4	-	-	-	0/4	1/5
hyperkeratosis	0/4	-	-	-	0/4	1/5 (1.0)
Nasal respiratory epithelium hyperplasia	0/5	-	-	0/5	1/5 (1.0)	5/5 (1.0)
Olfactory epithelium atrophy	0/5	-	-	0/5	0/5	2/5 (1.0)
metaplasia		-	-	0/5	0/5	3/5 (1.3)
Females: incidence (severity)						
Bone marrow hypocellularity	0/5	-	-	-	0/5	1/5 (1.0)
Lung bronchiolar hyperplasia	0/5	-	-	-	0/5	5/5 (1.2)
Nasal respiratory epithelium hyperplasia	2/5 min /mild	-	0/5	3/5 (1.0)	3/5 (1.7)	4/5 (1.5)
Olfactory epithelium metaplasia	0/5	-	-	-	0/5	2/5 (1.0)
Ovary atrophy	0/5	-	-	-	0/5	1/5 (2.0)
Uterus atrophy	0/5	-	-	-	0/5	1/5 (3.0)

Severity scores: 1 = minimal, 2 = mild, 3= moderate, 4 = severe

There were no liver lesions nor histopathology findings in testes.

NOAEL = 1000 ppm (90 / 95 mg/kg/d in males and females, respectively) based on respiratory epithelial hyperplasia in females and increased relative liver weight at 3000 ppm.

Oral (dietary)	0, 625, 1250, 2500, 5000,	Examinations: clinical chemistry, haematology, urinalysis, reproductive toxicity, gross pathology, organ weights, clinical

<table>
<tr>
<td>90 days

Mice, B6C3F1, 10/sex/dose

m-/p-cresol (purity>98%)

GLP

Similar to OECD 408

Reliability 1

Full study report evaluated

IUCLID 7.5.1.; NTP, 1992</td>
<td>10 000ppm

Equivalent to

Males: 0, 96, 194, 402, 776, 1513 mg/kg/d

Females: 0, 116, 239, 472, 923, 1693 mg/kg/d</td>
<td>pathology and histopathology.

No animals died during the study.

Clinical signs: rough hair coat in 3/10 females at 10 000 ppm.

Feed consumption was slightly decreased at 10 000 ppm. The changes in body weight and organ weights are summarised below.

<table>
<tr><th>ppm</th><th>0</th><th>625</th><th>1250</th><th>2500</th><th>5000</th><th>10000</th></tr>
<tr><td colspan="7">Males</td></tr>
<tr><td>Terminal body weight</td><td>100%</td><td>99%</td><td>101%</td><td>100%</td><td>99%</td><td>91%*</td></tr>
<tr><td>Terminal body weight gain</td><td>100%</td><td>98%</td><td>107%</td><td>100%</td><td>98%</td><td>76%*</td></tr>
<tr><td>Liver relative weight</td><td>100%</td><td>98%</td><td>104%</td><td>101%</td><td>112%*</td><td>123%*</td></tr>
<tr><td colspan="7">Females</td></tr>
<tr><td>Terminal body weight</td><td>100%</td><td>97%</td><td>98%</td><td>95%</td><td>96%</td><td>93%*</td></tr>
<tr><td>Terminal body weight gain</td><td>100%</td><td>94%</td><td>97%</td><td>89%</td><td>89%</td><td>87%</td></tr>
<tr><td>Liver relative weight</td><td>100%</td><td>99%</td><td>104%</td><td>99%</td><td>108%</td><td>116%*</td></tr>
</table>

Gross necropsy: no changes.

The histopathology findings of note are recorded below.

<table>
<tr><th>ppm</th><th>0</th><th>625</th><th>1250</th><th>2500</th><th>5000</th><th>10000</th></tr>
<tr><td colspan="7">Males: incidence (severity)</td></tr>
<tr><td>Nasal respiratory epithelium</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Glandular hyperplasia</td><td>1/10 (1.0)</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>2/10 (1.0)</td></tr>
<tr><td>hyperplasia</td><td>1/10 (1.0)</td><td>0/10</td><td>0/10</td><td>0/10</td><td>4/10 (1.0)</td><td>8/10 (1.0)</td></tr>
<tr><td colspan="7">Females: incidence (severity)</td></tr>
<tr><td>Nasal respiratory epithelium</td><td></td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Glandular hyperplasia</td><td>1/10 (1.0)</td><td>0/10</td><td>0/10</td><td>0/10</td><td>0/10</td><td>2/10 (1.5)</td></tr>
<tr><td>hyperplasia</td><td>2/10 (1.5)</td><td>0/10</td><td>0/10</td><td>3/10 (1.0)</td><td>2/10 (1.0)</td><td>5/10 (1.4)</td></tr>
</table>
Severity scores: 1 = minimal, 2 = mild, 3= moderate, 4 = severe

Reproductive end-points: no biologically-significant changes.

NOAEL = 2500 ppm (402 / 472 mg/kg/d in males and females, respectively), based on increased incidence of nasal respiratory epithelial hyperplasia and increased relative liver weight at 5000 ppm.</td>
</tr>
</table>

* Statistically significant, $p \leq 0.05$

The oral repeated-dose toxicity of *p*-cresol and *m-/p*-cresol has been investigated by dietary administration in mice.

In a 28-day study with *p*-cresol, all animals died in the high-dose group (30 000 ppm, equivalent to 1410 and 1590 mg/kg/d in males and females, respectively). Additionally, one male died in the 10 000 ppm group. At 10 000 ppm, both males and females had statistically significantly decreased terminal body weights and relative liver weights; the relative weight of kidneys and heart of males only at this dose were also affected. Weights of testes were unaffected and atrophy of the uterus did not occur. Some of the histopathology findings (renal tubule necrosis, liver necrosis) occurred only in the high-dose animals, all of which died early. Indications of respiratory and olfactory irritation, however, were reported at lower doses (from 1000 ppm), although these were generally scored as minimal to mild. The NOAEL for local effects was 300 ppm (50 mg/kg bw/d in males and 60 mg/kg bw/d in females) based on increased incidences of histopathology findings (respiratory epithelium hyperplasia) at 1000 ppm, whilst that for systemic effects was 1000 ppm (163/207 mg/kg/d in males and females, respectively) based on increased relative kidney weight at 3000 ppm.

A 28-day study in mice was also conducted with the *m-/p*-cresol mixture. There were no deaths, but body weight and body weight gains were statistically significantly reduced in the high-dose groups (10 000 and 30 000 ppm). Effects on the weights of liver and kidney were noted. The increased brain and testes weights were considered by the eMSCA to be secondary to the decreased body weight. Respiratory epithelial hyperplasia and olfactory epithelial lesions (consisting of atrophy and respiratory metaplasia) were observed at histopathology. Lesions in the lungs were also reported, comprising minimal to mild bronchiolar epithelial hyperplasia in all animals of the high-dose group. The lesions were particularly evident in the terminal bronchioles and showed epithelial thickening, loss of nuclear polarity and increased cytoplasmic basophilia. Bone marrow hypocellularity occurred in both sexes of the high-dose group. In one high-dose female, uterine and ovarian atrophy were observed. The NOAEL for systemic and local effects was 1000 ppm (90 / 95 mg/kg/d in males and females, respectively) based on respiratory epithelial hyperplasia in 3/5 females at 3000 ppm and a statistically significantly increased relative liver weight in males.

The *m-/p*-cresol mixture was further investigated in mice in a 90-day dietary study. There were no deaths and the overt signs of toxicity were not marked. However, there were statistically significant reductions in final body weights in the high-dose group animals (10 000 ppm). There were no gross changes at necropsy, and changes in organ weights were restricted to increased relative liver weights from 5000 ppm. Hyperplasia of the nasal respiratory epithelium were primarily reported in the anterior nasal sections and consisted of minimal to mild respiratory epithelial glandular hyperplasia. Hyperplastic areas were associated with single cell necrosis. There were no adverse effects on the investigated reproductive end-points (testes and epididymides weights, sperm motility and concentration, oestrus cycle length) at any dose in either sex. The NOAEL was 2500 ppm (402 / 472 mg/kg/d in males and females, respectively), based on increased incidence of nasal respiratory epithelial hyperplasia and increased relative liver weight at 5000 ppm.

The non-neoplastic findings in the carcinogenicity study are summarised in section 7.9.6.

7.9.4.1.3. Hamsters

The registration dossier also includes reference to a published study in hamsters (Hirose *et al.*, 1986). This provides information to support the evaluation of the carcinogenicity of *p*-cresol and so has been summarised here.

Male hamsters (15/group) were dosed with 0 and 1.5% (1100 mg/kg/d) *p*-cresol (purity > 98%) by dietary exposure for 20 weeks; one hour prior to sacrifice, ^{3}H-thymidine was injected intra-peritoneally into three hamsters per group. Body, liver and kidney weights

were recorded. The forestomach, glandular stomach and urinary bladder were analysed by histopathology and autoradiography. A statistically significantly increased incidence of mild (15/15) and moderate (10/15) fore-stomach hyperplasia was reported with 1.5% *p*-cresol compared with controls. The labelling index in the urinary bladder epithelium was increased compared with controls, although not with statistical significance; no histological changes such as inflammation, hyperplasia or tumorous lesions were observed.

7.9.4.2. Inhalation

One inhalation repeated-dose toxicity study was provided in the registration dossier under this section but it is of low reliability, as it contained minimal information. Female rats were exposed to a single concentration (0.01 mg/l) of *p*-cresol (purity not stated) for 4 months followed by a two-month recovery period. Clinical signs during exposure included loss of appetite, marked emaciation, decreased locomotor activity, and irritation of nose, eye and skin. During recovery, the eye, skin and nose irritation persisted and the body weights remained depressed. Further details were not provided.

7.9.4.3. Dermal

Two studies were submitted but provided very limited information, as they investigated only hair depigmentation and microscopic effects on hair and skin biopsies. Thus, they were not evaluated further by the eMSCA.

7.9.4.4. Summary and discussion of repeated-dose toxicity

Repeated-dose studies via the oral route on *p*-cresol and a 60:40 mixture of *m-/p*-cresol have been reported in the registration dossier. Some additional information on oral administration was identified by the eMSCA.

In repeated-dose toxicity studies in rats and mice, the principal finding was lesions that were consistent with irritation in the nasal cavity and respiratory tract. In the dietary studies this may have been attributable to inhalation of dust from the diet, although this is unconfirmed. A similiar finding, epithelial metaplasia of the trachea in the rat gavage 90-day study, might also have been a local effect. The 28-day study of m-/p-cresol in mice showed lung effects, in the form of bronchiolar epithelial hyperplasia, which would not be expected to be the result of inhaling a dust from the diet. A similar finding was reported in the mouse carcinogenicity study (see section 7.9.6), also with the m-/p-mixture. The authors of the carcinogenicity study postulated that p-cresol vapour from the feed was responsible for the nasal and bronchiolar effects, although the eMSCA notes that p-cresol has a relatively low vapour pressure . The low odour threshold of p-cresol (see section 7.12.1), however, indicates that the substance does volatilise. The eMSCA is aware of another case of lung effects in mice (alveolar haemorrhage) upon chronic dietary administration of an irritant substance (ipconazole). Lung effects (colour changes, congestion and haemorrhage) were also reported in the p-cresol two-generation study in rats, but only in animals that died before the scheduled sacrifice (section 7.9.7.1); it was not clear if these effects occurred pre- or post-mortem. Overall, the eMSCA concludes that the lung effects in mice after oral administration were a local rather than systemic effect. In hamsters, an increased incidence of mild and moderate fore-stomach hyperplasia was reported following dietary exposure; such effects with irritant/corrosive substances can normally be attributed to retention of the substance in the fore-stomach.

Decreases in kidney and liver weights were consistently reported. In some studies the kidney weight changes occurred at doses below those that caused reduced body weight. Although the absolute and/or relative kidney weights were reduced in all but the 90-day study in mice with *m-/p*-cresol mixture, the only histopathology finding was an increased incidence of nephropathy in all the male dose groups in the gavage 90-day study with *p*-cresol. There was not a clear dose-response relationship in the incidence or severity of the nephropathy, with the lesions being largely scored as minimal. Furthermore,

nephropathy was recorded in 20% of animals of the control group. Therefore, this isolated finding in one study is not considered to provide evidence of a treatment-related effect.

Liver weight was also consistently increased; this was without histopathology correlates in rats, but a small number of mice dosed with 30 000 ppm *p*-cresol in the 28-day study (all of which died early in this dose group) showed some liver lesions. Transiently elevated serum enzymes, elevated total bile acids and decreased 5'-nucleotidase in the 90-day study with *m-/p*-cresol provided some evidence of hepatocellular injury, but the urinalysis results did not support hepatic injury.

Effects on brain and testes relative weights occurred only at high-doses and were secondary to the general toxicity and decreased body weights at these doses. In a 28-day mouse study of the *m-/p*-cresol mixture, one female of the high-dose group had atrophy of the uterus and ovary; in rats, mild to moderate atrophy of the endometrium of the uterus was also reported in the high-dose group in the 28-day study with *p*-cresol, as was minimal to mild uterus atrophy in the high-dose group in the 90-day dietary study. In all cases, this was likely to be secondary to the general toxicity, particularly the weight loss and hence poor nutrition, that occurred in these animals.

The only treatment-related finding in the thyroid gland in rats was increased colloid in follicular cells when the *m-/p*-cresol mixture was administered for 28- and 90-days. The study authors reported that the biological significance of the lesion was uncertain, as it was not noted with the individual isomers, nor was it associated with overt follicular cell hypertrophy or hyperplasia. The authors postulated that increased colloid might have been secondary to decreased food consumption and body weights, since under-nutrition in rats has been associated with increased thyroid gland weights.

The NOAEL and LOAEL values from the available rat and mouse 28-day and 90-day repeated-dose toxicity studies are summarised below. These values did not highlight a noticeable difference in the potency of the individual *p*-isomer or the *m-/p-* mixture. Moreover, the lead effects were comparable, these being local effects on the nasal tissues and liver- and kidney-weight changes. Two effects were reported with the mixture but not with *p*-cresol alone: increased colloid in follicular cells of the thyroid gland and an increase in oestrus cycle length, both in rats.

Table 11. NOAEL and LOAEL values in rats and mice after oral administration of *p*-cresol and *m-/p*-cresol mixture (60:40)

Isomer	Study type	NOAEL (mg/kg/d)	LOAEL (mg/kg/d)	Effect
Rat				
p-	28-day dietary, F344 rats	242	769	Increased relative liver weight, hyperplasia of nasal respiratory epithelium (local effect)
p-	90-day gavage, Sprague Dawley rats	50	175	Increase in relative kidney weight, mild anaemia (females)
p-	90-day gavage neurotoxicity study, CD rats	175	600	Deaths, changes in some investigated parameters (lacrimation, palpebral closure, rales, laboured respiration, hypoactivity)
m-/p-	28-day dietary, F344 rats	90	261	Histopathology findings on thyroid gland (systemic), oesophagus and nasal tissues

				(local)
m-/p-	90-day dietary, F344 rats	123	241	Increased absolute kidney weight
Mouse				
p-	28-day dietary, B6C3F1 mice	Local = 50 Systemic = 163	Local = 163 Systemic = 469	Histopathology findings on nasal respiratory epithelium Increased relative kidney weight
m-/p-	28-day dietary in B6C3F1 mice	90	261	Increased relative liver weight (males), histopathology findings on nasal repiratory epithelium (local effect, females)
m-/p-	90-day dietary in B6C3F1 mice	402	776	Increased relative liver weight, histopathology findings on nasal respiratory epithelium (local effect)

7.9.5. Mutagenicity

This end-point was fully evaluated to inform on the concern for carcinogenicity.

7.9.5.1. *In vitro* studies

Several *in vitro* studies were submitted by the registrant; these were either study reports or published data. The information provided has been evaluated and where required the original study was requested.

Table 12. Summary of the available *in vitro* genotoxicity data

Method	Results	Remarks
Bacterial reverse mutation assay / Ames test		
Similar to OECD guideline 471 (plate incorporation method), GLP not stated *p*-cresol (98% purity) 0, 0.5, 5, 50, 500, 5000 µg/plate in DMSO 5 strains of *S. typhimurium* (TA98, TA100, TA1535, TA1537, TA1538) ± S9 from Sprague Dawley rats treated with Aroclor 1254. Pool & Lin, 1982	Cytotoxicity reported at 5000 µg/plate in the absence of S9 with TA1537, TA1538 and TA100 Cytoxicity reported at 5000 µg/plate in the presence of S9 with TA1535, TA1537, TA98 and TA100 There were no dose-related increases in the number of revertant colonies exposed to *p*-cresol across any of the strains in the absence or presence of S9. Positive controls were functional.	Key study Reliability 1 Full study report evaluated.
OECD guideline 471 (pre-incubation method) No data on GLP *p*-cresol (>97% purity)	*p*-cresol was negative in the absence and presence of S9 but not tested at limit concentration owing to limited solubility in water. Positive controls were functional	Reliability 2 Only 4 strains used and quantified data on colonies not

<table>
<tr><td>0, 3.3, 10, 33, 100, 333 µg/plate in water
4 strains of S. typhimurium (TA98, TA100, TA1535, TA1537)
± S9 from Syrian hamster or Sprague Dawley rat treated with Aroclor 1254
Haworth et al., 1983</td><td></td><td>provided.</td></tr>
<tr><td>OECD guideline 471. No data on GLP
p-cresol (commercial source)
up to 1 mg/plate (solubility limit) in water
5 strains of S. typhimurium (TA98, TA100, TA1535, TA1537, TA1538)
± S9 from Aroclor 1254 induced rat livers
Nestmann et al., 1980</td><td>Negative but limited solubility in water did not allow for testing at bacterially-toxic concentrations.</td><td>Reliability 2
Doses and quantification of colonies not provided</td></tr>
<tr><td>No data on GLP, no guideline
p-cresol (no further data)
Up to 30µmol/plate
± S9 (origin not stated)
4 strains of S. typhimurium (TA98, TA100, TA1535, TA1537)
Florin et al., 1980</td><td>p-cresol was cytotoxic at 30 µmol/plate
p-cresol was negative under the conditions of the test</td><td>Reliability 4
Information insufficient for assessment (migrated data set)</td></tr>
<tr><td colspan="3">Mouse lymphoma assay</td></tr>
<tr><td>GLP and OECD guideline 476 (mouse lymphoma cells L5178Y TK+/-)
p-cresol (99.8% purity)
Without S9: 51.1, 102, 153, 204, 307 and 409 µg/ml in DMSO for 4 hours
With S9: 0.256, 0.511, 0.767, 1.02, 1.53 and 3.07µg/ml in DMSO for 4 hours
Positive control –S9- ethylmethane sulphonate (EMS) (0.25 and 0.4 µL/ml)
Positive control +S9- 3-methylcholantrene (MCA) (2.5 and 4.0 µg/ml)
S9 from rat liver
IUCLID 7.6.1.</td><td>In a preliminary study, p-cresol was excessively toxic at 511 µg/ml without metabolic activation and at 5.11 µg/ml with metabolic activation.
In the main test without metabolic activation, a range of cytotoxicity levels was induced across the concentration range, with relative growths of 72.6% to 3.6%. In the main test with metabolic activation, cytotoxicity ranged from none to very high (relative growths 106.7% to 4.8%).
<table>
<tr><th></th><th>Test concentration</th><th>Mutant frequency</th></tr>
<tr><td rowspan="9">-S9</td><td>0</td><td>21.7</td></tr>
<tr><td>51.1</td><td>18.5</td></tr>
<tr><td>102</td><td>19.6</td></tr>
<tr><td>153</td><td>28.6</td></tr>
<tr><td>204</td><td>23.2</td></tr>
<tr><td>307</td><td>26.8</td></tr>
<tr><td>409</td><td>33.6</td></tr>
<tr><td>EMS 0.25</td><td>450.3</td></tr>
<tr><td>EMS 0.4</td><td>388.6</td></tr>
<tr><td rowspan="2">+S9</td><td>0</td><td>28.0</td></tr>
<tr><td>0.256</td><td>23.3</td></tr>
</table></td><td>Key study
Reliability 2
Full evaluation of study.
No differentiation between small and large colonies.</td></tr>
</table>

		0.511	22.1
		0.767	23.3
		1.02	25.9
		1.53	29.5
		3.07	28.3
		MCA 2.5	447.9
		MCA 4.0	333.7
	Overall, *p*-cresol was negative with and without S9.		
Chromosomal aberration assay			
OECD Guideline 473, GLP *p*-cresol (99.8% purity) Vehicle- DMSO Chinese Hamster Ovary cells Without S9- 100, 150, 200, 301 µg/ml for 20 hours With S9- 301, 601, 902 µg/ml for 20 hours With S9- 150, 225, 300 µg/ml for 10 hours in two tests Cytotoxicity is measured by visual inspection of monolayer and floating large or dead cells. IUCLID 7.6.1.	Cytotoxicity was observed at ≥301 µg/ml without S9 and ≥ 1000 µg/ml with S9 during the preliminary test. Average percentage of cells with aberrations			
	Test / Test substance / Cells scored / % cells with aberrations / % cells with >1 aberration			
	-S9 20 h / 0 / 200 / 1.0 / 0.0			
	100 / 200 / 6.5* / 1.5			
	150 / 200 / 11.0* / 1.5			
	200 / 150 / 7.3* / 0.0			
	301 / 200 / 8.0* / 2.0			
	MMC / 25 / 44.0* / 20.0			
	+S9 10 h / 0 / 200 / 0.5 / 0.0			
	150 / 200 / 2.0 / 0.5			
	225 / 200 / 1.5 / 1.0			
	300 / 200 / 3.0 / 0.0			
	CP / 25 / 32.0* / 0.0			
	+ S9 20 h / 0 / 200 / 1.5 / 0.0			
	301 / 200 / 18.0* / 14.0*			
	601 / 200 / 40.5* / 29.0*			
	902 / - / TOXIC / TOXIC			
	CP / 100 / 25.0* / 10.0*			
	Overall, p-cresol induced chromosome aberrations with and without metabolic activation.			
	Key study Reliability 1 Full study evaluated-compliant with guidelines at the time of study performance.			
SCE assay				
Non-guideline and no data on GLP *p*-cresol (>99% purity) Male human fibroblasts 0, 0.008, 0.8, 4 and 8mM *p*-cresol in ethanol and 10 and 30mM in MEM Cheng & Kligerman, 1984	Cytotoxicity measured by cell cycle progression No metabolic activation Decrease in cell cycle progression at 8mM or greater, indicating some cytotoxicity. *p*-cresol did not induce significant increases in SCE frequency compared with controls			Reliability 2 Only –S9 tested

The genotoxicity of *p*-cresol has been investigated in a variety of *in vitro* assays.

p-Cresol was negative in the four available bacterial reverse mutation tests and in a GLP- and guideline-compliant mouse lymphoma assay.

A GLP- and guideline-compliant chromosomal aberration test with Chinese hamster ovary cells was positive, indicating that *p*-cresol induced aberrations in mammalian cells *in vitro*. The percentage of cells with aberrations was greater with metabolic activation for 20 hours than without activation.

In a sister chromatid exchange assay with human cells, *p*-cresol was negative. It was also reported to be negative in an additional sister chromatid exchange assay, but that study summary lacked data on positive and negative controls, metabolic activation and cytotoxicity. Several other *in vitro* studies were reported in the registration dossier but were of limited use in assessing the genotoxic potential of *p*-cresol. Two unscheduled DNA synthesis assays with human cells were positive for thymidine incorporation but lacked validation of the method or contained insufficient information on methodology and results. *p*-Cresol was positive for adduct formation when incubated with calf thymus DNA, but the assay was not a validated test method.

Overall, *p*-cresol was positive for the induction of chromosome aberrations in mammalian cells *in vitro*. It did not induce gene mutations in bacteria or mammalian cells *in vitro*.

7.9.5.2. *In vivo* studies

Four *in vivo* studies were submitted, three in mice and one in *Drosophila melangastor*. The key studies are reported in the table below.

Table 13. Summary of *in vivo* genotoxicity studies

<table>
<tr><th>Method</th><th>Results</th></tr>
<tr><td colspan="2">Micronucleus test</td></tr>
<tr><td>Non-guideline, not GLP

m/p cresol mix at 60:40 ratio respectively

Male and female B6C3F1 mice (10/sex/dose group)

0, 625, 1250, 2500, 5000 and 10 000ppm mix for 13 weeks in the diet (part of the 90-day studies reported in section 7.9.4.)

Peripheral blood obtained at termination by cardiac puncture

Normochromatic and polychromatic erythrocytes were examined. 10 000 normochromatic erythrocytes were scored and the percentage polychromatic erythrocytes calculated from total erythrocyte population.

Reliability 2

Full study report evaluated

IUCLID 7.6.2; NTP, 1992</td><td>Toxicity to the bone marrow was demonstrated in the repeated-dose toxicity investigations (section 7.9.4.).

Males
<table><tr><th>Dose</th><th>Micronucleated NCEs/ 1000 NCEs (mean ± SEM)</th><th>p-value</th><th>% PCEs (mean ± SEM)</th></tr><tr><td>0</td><td>0.94 ± 0.14</td><td>-</td><td>1.03 ± 0.09</td></tr><tr><td>625</td><td>0.82 ± 0.13</td><td>0.77</td><td>1.17 ± 0.09</td></tr><tr><td>1250</td><td>0.89 ± 0.11</td><td>0.61</td><td>1.17 ± 0.06</td></tr><tr><td>2500</td><td>0.8 ± 0.09</td><td>0.81</td><td>1.31 ± 0.11</td></tr><tr><td>5000</td><td>0.95 ± 0.08</td><td>046</td><td>1.07 ± 0.1</td></tr><tr><td>10 000</td><td>0.98 ± 0.1</td><td>0.39</td><td>1.31 ± 0.08</td></tr></table>
Females
<table><tr><th>Dose</th><th>Micronucleated NCEs/ 1000 NCEs (mean ± SEM)</th><th>p-value</th><th>% PCEs (mean ± SEM)</th></tr><tr><td>0</td><td>0.69 ± 0.08</td><td>-</td><td>1.27 ± 0.11</td></tr><tr><td>625</td><td>0.6 ± 0.05</td><td>0.79</td><td>1.15 ± 1.06</td></tr><tr><td>1250</td><td>0.53 ± 0.08</td><td>0.94</td><td>1.06 ± 0.07</td></tr><tr><td>2500</td><td>0.55 ± 0.07</td><td>0.91</td><td>1.08 ± 0.1</td></tr><tr><td>5000</td><td>0.50 ± 0.06</td><td>0.96</td><td>0.93 ± 0.06</td></tr><tr><td>10 000</td><td>0.55 ± 0.09</td><td>0.91</td><td>1.08 ± 0.09</td></tr></table>
No increase in the frequency of micronucleated erythrocytes was seen in male or female mice.</td></tr>
</table>

Dominant lethal assay	
OECD guideline 478, GLP *p*-cresol (99.8% purity) 25 male mice (ICR) / dose group 50 females / group 0, 100, 275, 550 and 650 mg/kg bw in corn oil by gavage Males mated with females for 6 weeks post dosing Positive control: triethylenemelamine by IP at 0.3 mg/kg Reliability 1 IUCLID 7.6.2.	Deaths and clinical signs *650 mg/kg bw/d* Removed from the study during the first week owing to toxicity (rapid breathing, languid with mild convulsions and squinted eyes, prostrate and scruffy coats) and deaths (10/25). *550 mg/kg bw* 6/25 males died. Signs of clinical toxicity included rapid breathing, languid and scruffy coats. *275 mg/kg bw/d* No deaths reported Signs of clinical toxicity: scruffy coats *100 mg/kg bw/d* 1 male (week 4) and 3 females (week 6) died *Positive control* 1 female died during gestation *Fertility indices and implantation loss*

Wk		Fertility index	Total implants	% pregnant with ≥ 1 dead implant	% pregnant with > 1 dead implant
1	0	0.82	484	46.3	19.5
	100	0.86	515	46.5	18.6
	275	0.86	518	39.5	18.6
	550	0.54*	336	48.1	11.1
	+ve	0.86	452*	93.0**	79.1**
2	0	0.9	527	51.1	15.6
	100	0.8	468	50.0	17.5
	275	0.66*	385	45.5	18.2
	550	0.82	410	47.2	16.7
	+ve	0.54*	231*	100.0**	100.0**
3	0	0.88	579	50.0	13.6
	100	0.9	579	55.6	15.6
	275	0.88	537	45.5	20.5
	550	0.91	474*	45.0	5.0
	+ve	0.82	453*	95.1**	90.2**
4	0	0.86	479	32.6	7.0
	100	0.9	555	52.3	4.5
	275	0.82	489	43.9	14.6
	550	0.82	456	38.9	25.0**
	+ve	0.68*	424	61.8**	26.5**

There were no changes reported with *p*-cresol or the positive control in weeks 5 and 6.

p-Cresol was not a germ cell mutagen in this assay

Four *in vivo* studies were submitted by the registrant on *p*-cresol or *m/p*-cresol mix: a micronucleus assay (key study), a dominant lethal assay (key study), a sex-linked recessive lethal test and a sister chromatid exchange assay.

A micronucleus test was conducted at the end of the 13-week toxicity study with *m-/p*-cresol (section 7.9.4.). After 13 weeks of dietary administration of the mixture, peripheral blood samples were obtained from male and female mice to determine the frequency of micronuclei and the polychromatic to normochromatic erythrocyte ratio. A detailed description of the assay protocol is provided by MacGregor *et al.*, 1990). There was no increase in micronucleus formation in the mouse with the *m-/p*-cresol mixture (maximum dose 10 000ppm or 1693 mg/kg/d of the mixture, equivalent to 677 mg/kg/d *p*-cresol) compared with concurrent negative controls. The dose of the cresol mixture administered exceeds the limit dose of 1000 mg/kg/d for a treatment duration longer than 14 days that is recommended in OECD guideline 474. In the 13-week mouse study, systemic toxicity was indicated by clinical signs, decreased terminal body weight (by 9%) / body weight gain at 10 000ppm and increased relative liver weight from 5000 ppm. Histopathology changes in the bone marrow in repeated-dose toxicity studies in rats and mice (section 7.9.4) indicated that *p*-cresol reached the target tissue; these changes were reported at 2570 mg/kg/d *m-/p*-cresol in a 28-day mouse study, 1410 mg/kg/d *p*-cresol in a 28-day mouse study and from 769 mg/kg/d *p*-cresol in a 28-day rat study. Taking into account also the extensive absorption after oral administration of *p*-cresol and, based on the somewhat limited information, its widespread distribution (section 7.9.1.) and the prolonged duration of exposure, the eMSCA concludes that *p*-cresol would have reached the bone marrow and thus that the negative result in this micronucleus test was valid.

The dominant lethal assay was performed to GLP and OECD guideline 478. No changes in implantation loss were reported in the *p*-cresol-treated groups compared with negative controls, indicating that *p*-cresol was not a germ cell mutagen in this assay.

p-Cresol was also negative in a sex-linked recessive lethal test in *Drosophila melangastor* and a sister chromatid exchange test in mice. Both of these studies had limitations, however, and were poorly reported.

7.9.5.3. *Summary* and discussion of mutagenicity

p-Cresol was positive in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells both with and without metabolic activation. It did not show evidence of mutagenicity in bacterial or mammalian cells *in vitro*.

The potential to induce clastogenicity *in vivo* was investigated in a micronucleus test in mice, in which the frequency of micronuclei in the peripheral blood was determined after 13 weeks of administration of *m-/p*-cresol mixture. The micronucleus test was negative at the maximum dose tested of *m-/p*-cresol mixture (1693 mg/kg/d), which equates to 667 mg/kg/d *p*-cresol. In the context of 1000 mg/kg/d being the limit dose in OECD guideline 474 for treatment durations of 14 days or longer, exposure to 667 mg/kg/d for 13 weeks is a high dose; moreover, there was evidence of systemic and bone marrow toxicity in the repeated-dose studies. The *in vivo* micronucleus test is therefore sufficient to negate concerns from the *in vitro* chromosomal aberration assay. *p*-Cresol was not a germ cell mutagen under the conditions of the available dominant lethal test.

It has been postulated that the observed *in vitro* genotoxicity with *p*-cresol might be due to the metabolic formation of reactive intermediates such as quinone-methide. In rabbits, metabolites resulting from these intermediates were found in the urine in only limited amounts. Data on the metabolism of cresols in other species, including man, is limited. However, based on the negative *in vivo* genotoxicity tests, and assuming that detoxifying and conjugating mechanisms are efficiently trapping these intermediates, it has previously been assumed that the cresols probably do not pose a genotoxic hazard in humans (DECOS, 1998).

Overall, the eMSCA concludes that *p*-cresol is not genotoxic *in vivo*.

7.9.6. Carcinogenicity

As carcinogenicity was an initial concern, the information available on this end-point was fully evaluated.

Carcinogenicity studies were available in rats and mice with the 60:40 *m-/p*-cresol mixture.

Table 14. Summary of carcinogenicity studies

<table>
<tr><th>Method</th><th>Doses</th><th>Results</th></tr>
<tr><td>Oral (dietary)

105 weeks

Rats, male F344/N, 50/dose group

m-/p-cresol mixture (60:40)

OECD 451, GLP

Reliability 1

IUCLID 7.7; NTP, 2008

Full study report evaluated</td><td>0, 1500, 5000, 15 000 ppm

Equivalent to

0, 70, 230 and 720 mg/kg/d m-/p- (60:40) cresol mixture

Feed: NTP 2000 open formula meal</td><td>Only male rats were included in the study.

Animals surviving until the end of the study: 33, 34, 33, 31 at 0, 1500, 5000 and 15 000 ppm. Mean survival (days): 703, 696, 671, 684.

Non-neoplastic findings

Body-weights of the 15 000 ppm group were lower than the controls throughout the study, culminating in a final body weight that was 15% lower than that of the controls. Apart from during the first week, food consumption was not adversely affected in this or any other treatment group. Otherwise, there were no overt clinical signs of toxicity.

The histopathology findings of note are summarised below
<table>
<tr><th>ppm</th><th>0</th><th>1500</th><th>5000</th><th>15 000</th></tr>
<tr><td>Kidney: pelvis transitional epithelium hyperplasia (severity)</td><td>0/50</td><td>0/50</td><td>2/49 (2.0)</td><td>8/50* (1.9)</td></tr>
<tr><td>Kidney: renal tubule hyperplasia</td><td>5/50 (1.0)</td><td>0/50</td><td>1/50</td><td>1/50 (2.0)</td></tr>
<tr><td>Nephropathy incidence (severity)</td><td>47 (1.4)</td><td>48 (1.4)</td><td>46 (1.7)</td><td>49 (2.1)</td></tr>
<tr><td>Nose: respiratory epithelium hyperplasia</td><td>3/50</td><td>17/50</td><td>31/49</td><td>47/49</td></tr>
<tr><td>Nose: goblet cell hyperplasia</td><td>23/50</td><td>40/50</td><td>42/50</td><td>47/50</td></tr>
<tr><td>Nose: respiratory epithelium metaplasia</td><td>0/50</td><td>1/50</td><td>19/50</td><td>28/50</td></tr>
<tr><td>Nose: inflammation</td><td>17/50</td><td>19/50</td><td>19/50</td><td>28/50</td></tr>
<tr><td>Liver: eosinophilic foci</td><td>1/50</td><td>0/50</td><td>2/49</td><td>12/50</td></tr>
</table>
Severity scores: 1 = minimal, 2 = mild, 3= moderate, 4 = severe

Neoplastic findings

The neoplastic findings are summarised below.
<table>
<tr><th>ppm</th><th>0</th><th>1500</th><th>5000</th><th>15 000</th></tr>
<tr><td>Kidney</td><td></td><td></td><td></td><td></td></tr>
<tr><td>Renal tubule adenoma</td><td>0/50</td><td>0/50</td><td>0/50</td><td>4/50 8%</td></tr>
</table></td></tr>
</table>

<table>
<tr>
<td></td>
<td></td>
<td>
<table>
<tr><td>Lipoma</td><td>0/50</td><td>1/50</td><td>0/50</td><td>1/50</td></tr>
</table>

The first incidence of renal adenoma was recorded at 725 days.

Historical control data from 5 feeding studies in male F344/N rats, same laboratory, up until 2/3/07 (NTP 2000 diet):
• Renal adenomas = 1/297 animals (0.3%); range 0-2%
• Lipomas = 0 / 297 animals
Historical control data from 69 NTP studies conducted between 1977 and approximately 2004 for male F344/N rats = 16/1627 (0.98%, range 0-6%) by standard histopathology sections. Extended evaluation of 13 NTP studies conducted before 1994 = 29/649 (4.47%, range 0 – 16%) in male F344 rats Eustis et al., 1994.

NOAEL for non-neoplastic systemic effects = 1500 ppm (70 mg/kg/d) based on liver and kidney effects at 5000 ppm
</td>
</tr>
<tr>
<td>Oral (dietary)

105 weeks

Mice, female B6C3F1 mice, 50/dose group

m/p cresol mixture (60:40)

OECD 451, GLP

Reliability 1

Full study report evaluated.

IUCLID 7.7; NTP, 2008</td>
<td>0, 1000, 3000, 10 000 ppm

Equivalent to

0, 100, 300 and 1040 mg/kg/d m/p-cresol mixture (60:40)

Feed: NTP 2000 open formula meal</td>
<td>
Only female mice included in the study.

Animals surviving until the end of the study: 41, 43, 44, 42 at 0, 1000, 3000 and 10 000 ppm. Mean survival (days): 696, 717, 719, 705.

Non-neoplastic findings

Mean body weights of the 3,000 and 10,000 ppm groups were less than those of the control group after weeks 12 and 9, respectively, and decreased to 88% and 75% that of the control group, respectively, by the end of the study. Overall feed consumption for the 10,000 ppm group was decreased by 13% (attributed to poor palatability) while overall feed consumption by the 1,000 and 3,000 ppm groups was unaffected. There were no clinical findings related to exposure to cresols. Otherwise, there were no overt clinical signs of toxicity.

Histopathology findings of note are summarised below.
<table>
<tr><th>ppm</th><th>0</th><th>1000</th><th>3000</th><th>10000</th></tr>
<tr><td>Lung: bronchiole hyperplasia (severity)</td><td>0/50</td><td>42/50 (1)</td><td>44/49* (2)</td><td>47/50* (3)</td></tr>
<tr><td>Nose: respiratory epithelium hyperplasia</td><td>0/50</td><td>0/50</td><td>28/49* (1.3)</td><td>45/49* (2.2)</td></tr>
<tr><td>Thyroid gland: follicular degeneration</td><td>7/48 (2)</td><td>24/48* (1.8)</td><td>24/49* (1.8)</td><td>21/50* (1.8)</td></tr>
<tr><td>Liver: eosinophilic foci</td><td>1/50</td><td>0/50</td><td>2/49</td><td>12/50*</td></tr>
</table>
Severity scores: 1 = minimal, 2 = mild, 3= moderate, 4 = severe

Neoplastic findings

The neoplastic findings are summarised below.
<table>
<tr><th>ppm</th><th>0</th><th>1000</th><th>3000</th><th>10000</th></tr>
<tr><td>Squamous cell</td><td>0/50</td><td>1/50</td><td>1/49</td><td>10/50*</td></tr>
</table>
</td>
</tr>
</table>

		papilloma of fore-stomach		2%	2%	20%
		First occurrence of squamous cell papilloma of fore-stomach 713 days at 10 000ppm, 728 days (termination) for other treatment groups. Historical control data were from 6 feeding studies with B6C3F1 mice as of 2/3/07: 6/350 (1.8%); range 0-6% NOAEL for non-neoplastic systemic effects = 1000 ppm (100 mg/kg/d) based on decreased terminal body weight at 3000 ppm				

* Statistically significant ($p \leq 0.05$)

Two carcinogenicity studies were available to address the carcinogenicity of *p*-cresol, one in rats and one in mice. A cell transformation assay was also available but as this assay is not considered to be predictive of carcinogenicity it has not been evaluated further.

Rats

In the rat study (only males investigated), an increase in the incidence of renal tubule adenoma was reported (8%, 4/50, none in any other group) at 720 mg/kg/d of the *m*-/*p*-cresol mixture, which equates to 288 mg/kg/d *p*-cresol. The increased incidence was not statistically significant (p = 0.054 by poly-3 pairwise comparison[11] between control and high-dose groups). This tumour type was outside the laboratory's concurrent historical control range (0 – 2%, mean 0.3%) and was accompanied by transitional changes of the kidney epithelium. The kidneys were initially sectioned to a thickness of 4 to 6 µm and stained with haematoxylin and eosin; this analysis revealed three adenomas. An extended evaluation was then undertaken, during which additional sections of both kidneys were obtained from each rat and step-sectioned at 1 mm intervals. Three (left kidney) or four (right kidney) sections were examined for each rat. One additional renal tubule adenoma was detected by this extended analysis; four other animals had renal tubule hyperplasia (three in control animals and one in the mid-dose group). The slides were reviewed by the NTP Pathology Working Group.

Single cases of lipoma were reported in the low- and high-dose group. Lipomas are relatively common benign tumours that are not thought to progress to malignancy. Given that the incidence was so low and without a dose-response relationship, these tumours are not considered to be related to treatment. There were no other treatment-related neoplastic findings in male rats.

Non-neoplastic findings comprised histopathology changes in the nasal passages from 1500 ppm that were indicative of irritation (attributed to inhalation exposure to *p*-cresol vapour from the diet; an alternative explanation might be inhalation of dust from the diet) and an increased incidence of eosinophilic focus of the liver in the high-dose group. A dose-related increase in renal tubule hyperplasia did not occur, but there was an increase in the incidence of hyperplasia of the transitional epithelium in the high-dose group; the authors considered this to be secondary to the slight increase in the severity of nephropathy in this group compared with the controls (Sanders *et al.*, 2009).

Mice

[11] The Poly-3 test accounts for differential mortality in animals that do not reach terminal sacrifice.

In the mouse study (only females investigated), the incidence of squamous cell papilloma of the fore-stomach was increased at the highest dose tested of *m-/p*-cresol mixture. This dose equated to 10 000 ppm (1040 mg/kg/d) in total or 416 mg/kg/d *p*-cresol (60: 40 ratio). The incidence of fore-stomach squamous cell papilloma (10/50, 20%) reported was statistically significantly increased compared with concurrent controls and was outside the historical control range (1.8% mean ± 1.3%; range 0-6%). This finding was not associated with changes in histopathology but it was accompanied by general toxicity which manifested as a decrease in body weight of 15%. Hyperplasia of the fore-stomach of hamsters in a 20-week study (section 7.9.4) was consistent with this finding in the mouse study. No other neoplastic findings were reported in mice.

In terms of non-neoplastic effects, respiratory epithelium hyperplasia was reported in the mid-and high-dose groups. Besides these irritant effects in the nasal passages, lung effects were observed in the form of hyperplasia of the bronchioles in all treatment groups, with the severity increasing with increasing dose. This finding is discussed in the context of repeated-dose toxicity in section 7.9.4.4.

Minimal to mild thyroid follicular degeneration was reported in all the treatment groups. Neither the incidence nor severity, however, increased with increasing doses; rather, the severity was slightly less in the treated groups than in the controls. The degeneration was characterised by areas of pale-staining colloid. As the thyroid was not a target organ in studies with *p*-cresol alone and there was a very high background incidence, the eMSCA concludes that this did not indicate toxicity to the thyroid from *p*-cresol administration.

7.9.6.1. Summary and discussion of carcinogenicity

p-Cresol was not genotoxic *in vivo* (section 7.9.5). In the two available carcinogenicity studies, the only tumour findings that showed a dose-response relationship were squamous cell papilloma of the fore-stomach in female mice and renal tubule adenomas in male rats in the high-dose groups.

Squamous cell papilloma of the fore-stomach in female mice

The relevance of rodent fore-stomach lesions (specifically tumours) for human risk assessment has been reviewed by RIVM (Pronk, 2003). The rodent stomach consists of two anatomically distinct parts: a non-glandular fore-stomach; and a glandular stomach. The rodent glandular stomach is structurally and functionally similar to the stomach of other mammalian non-rodent species, including humans. In contrast, the fore-stomach has no counterpart in humans (nor several test laboratory species, including dogs and rabbits). The fore-stomach forms a continuum with the oesophagus and is lined with keratinised, stratified squamous epithelium; humans have comparable squamous epithelial tissues in the oral cavity and upper two-thirds of the oesophagus. A difference between the rodent oesophagus and that of most mammals (including humans) is that the rodent oesophagus (and also the fore-stomach) does not contain mucosal glands that secrete mucus to aid the passage of food; however, the keratin coating of oesophageal epithelial cells is more pronounced in rodents than humans and provides further protection against chemical insults. Another difference between the species is that rodents lack a vomiting reflex, whereas humans are able to vomit to rid themselves of irritating substances. The main function of the fore-stomach is storage and triturition of food prior to digestion in the glandular stomach. Because of this storage function, the passage of food through the fore-stomach is much slower than through the human mouth and oesophagus; there is therefore a longer time for interaction of ingested chemicals and epithelial cells in the fore-stomach than in the human mouth and oesophagus. Although the epithelium of the rodent oesophagus and fore-stomach are morphologically identical and continuous, it is rare for oesophageal lesions (tumours, epithelial hyperplasia) to occur even if fore-stomach tumours are observed (Pronk, 2003); this could be explained by the rapid passage of ingested material through the oesophagus, and/or the difference in physiological conditions (e.g. pH, surface population

of bacteria and yeast). Overall, RIVM's conclusion was that fore-stomach effects (specifically, tumours) induced by non-genotoxic substances only after oral administration are not relevant for humans.

Considering the differences in the physiology of the gastrointestinal tract between rodents and humans, and in this context the irritant nature of *p*-cresol, the eMSCA concludes that the fore-stomach tumours in mice do not translate to a carcinogenic hazard in humans.

Renal tubule adenomas in male rats

In an NTP carcinogenicity study that was published in 2008, renal tubule adenomas were reported in 8% of male rats of the high-dose group, with no cases in any other group nor in female mice. A treatment-related increase in the incidence of atypical tubule hyperplasia (ATH) was not apparent. There was a slight dose-related increase in the severity of chronic progressive nephropathy (CPN), from a score of 1.4 (minimal/mild) in controls to 2.1 (mild) in the high-dose group. The NTP concluded that the rat carcinogenicity study provided equivocal evidence of a carcinogenic effect of *m-/p*-cresol.

Lock & Hard, 2004) placed 69 chemicals that induced renal tumours in NTP carcinogenicity studies into one of several categories, based on the available information on the chemicals' mode of action. The information on *m-/p*-cresol is assessed in relation to these categories.

Category 1. Chemicals inducing renal tumours through direct interaction of the parent compound or metabolite with renal DNA

p-Cresol and *m-/p*-cresol were negative in the available *in vivo* genotoxicity studies. Moreover, direct-acting chemicals often produce renal tumours in mice as well as rats; the tumour incidence is often high; the latency period can be relatively short; metastases to other organs are sometimes seen; and the renal tumours are associated with a clear background of ATH that is not linked to the presence of CPN. The tumour findings with *m-/p*-cresol did not match this pattern.

Category 2. Chemicals inducing renal tumours through indirect DNA reactivity mediated by oxidative stress

Chemicals that act via this mechanism are usually positive in some short-term genotoxicity tests. They are able to induce high incidences of renal tumours in both rats and mice, and both sexes can be affected. For example, potassium bromate produced about an 80% incidence of renal tumours in male and female F344 rats. This pattern of findings was not apparent with *m-/p*-cresol.

Category 3. Chemicals inducing renal tumours following conjugation with glutathione and subsequent enzymatic activation to a reactive species

A number of halogenated alkenes and halogenated aromatic compounds undergo metabolism via conjugation with glutathione. The formation of glutathione conjugates targets these chemicals to the kidneys, where they can accumulate in renal tubule cells and then undergo activation to form a chemically-reactive species, ultimately leading to renal tubule necrosis and compensatory cell regeneration. These chemicals also tend to increase the incidence and severity of CPN and produce a relatively low incidence of renal tubule tumours and carcinomas. Some of the glutathione-derived metabolites have produced mutagenic responses in *S. typhimurium* strains with metabolic activation. Of the chemicals that Lock and Hard concluded were in this group, other findings included: renal tubule cytotoxicity (for example, selective necrosis of the *pars recta* of the proximal tubule following acute and sub-chronic administration) and hence regenerative cell proliferation; metastasis; renal tubule degeneration; hepatocellular carcinomas; renal

tubule dilatation and karyomegaly in rats and mice; renal tubule carcinomas; and renal tumours in mice.

Given the metabolism of *p*-cresol via glutathione and other pathways to reactive intermediates and their extensive urinary excretion, it is feasible that *p*-cresol could induce renal tumours via this mode of action. The severity of CPN was slightly increased by exposure to *m-/p*-cresol and the incidence of adenomas was low. However, *p*-cresol is not halogenated and there were no other findings in the repeated-dose toxicity or carcinogenicity studies that indicated that this mode of action was involved. The NTP (2008) proposed that the adenomas in the cresol study could have arisen by a similar mode of action to that proposed for hydroquinone. Hydroquinone markedly increases the number of renal tubule adenomas when administered to male F344/N rats at nephrotoxic doses, an effect attributed to a minor but potent toxic and redox-active species. The NTP noted that the formation of benzoquinones from *m*- and *p*-cresol and quinone methide from *p*-cresol is inferred from the identification of specific glutathione conjugates formed in rat and human liver microsomal incubations (section 7.9.1.). The NTP considered, however, that the potential for the formation of quinone-like reactive metabolites from cresols should be much lower than for hydroquinone itself and should thus result in a weaker neoplastic response. Interestingly, Lock & Hard (2004) placed hydroquinone in a different mode-of-action category (see below). Overall, in the absence of any indications that the cresols were nephrotoxic in the available studies and the absence of other relevant tumour findings, the eMSCA concludes that this mode of action is unlikely to play a major role in the induction of renal tubule tumours.

Category 4. Chemicals inducing renal tumours via direct cytotoxicity and sustained tubule cell regeneration

Chemicals that are not DNA reactive but that cause cellular toxicity to the rodent renal tubule, thereby stimulating repair and regenerative cell proliferation, were grouped by Lock and Hard (2004) into one of two categories: category 4 where the regenerative response was to direct cytotoxicity elicited by the chemical or its metabolites; and category 5 where the regeneration was in response to indirect cytotoxicity caused by cellular lysosomal overload. In both cases, chemicals tended to produce a low incidence of renal tubule tumours, with a long latency and usually only in the male rat. Tumour metastasis is uncommon but a moderate level of karyomegaly in the region that was affected by the injury and regeneration is a usual accompaniment at the chronic time-points.

Two chemicals were placed in category 4. Besides the aforementioned effects, the findings with these chemicals included nephrotoxicity localised to the proximal convoluted tubule cells in mice; also in mice, a strong correlation of nephrotoxicity, sustained regenerative tubule cell proliferation and the occurrence of renal tubules; in rats, evidence of persistent mild to moderate cellular changes that indicated sustained tubule damage accompanied by regeneration; also in rats, renal tubule hyperplasia, renal tubule epithelial cell proliferation, proximal tubule cell loss via apoptosis and cell regeneration through sustained simple tubule hyperplasia; site concordance between the small proliferative lesions and the deep cortical zone of tubule cell injury. With one chemical, the 'exceptionally aggressive nature' of the renal tumours was highlighted, these being 'highly malignant, invasive carcinomas'. There was no indication from the available data that *m-/p*-cresol caused direct nephrotoxicity that resulted in sustained regeneration; although renal tubule necrosis was reported in one mouse study, it only occurred at very high doses that resulted in the death of all the animals.

Category 5. Chemicals inducing renal tumours via indirect cytotoxicity and sustained tubule cell regeneration associated with α_{2u}-globulin accumulation

This mode of action is specific to male rats. A number of chemicals that act via this mode of action have produced an increased incidence of renal tubule tumours of up to 30%. Besides non-genotoxicity, specific histological criteria must be met for this mode of action

to be assigned to a chemical (Swenberg & Lehman-McKeeman, 1999); these have gained international regulatory acceptance.

The available information on *m-/p*-cresol indicates that some of these criteria were not met: accumulation of granular casts, tubule dilation, enhanced cell replication after 3-6 weeks; tubule hyperplasia and linear mineralisation in chronic studies. Investigations to inform on other characteristic findings were not available: hyaline droplet accumulation within 24 hours; single-cell necrosis and exfoliation in the P2 segment epithelium after 5 days; identification of the protein accumulating in tubule cells as α2u-globulin. On balance, it seems unlikely that this mode of action was responsible for the renal tubule adenomas in the high-dose group.

Category 6. Chemicals increasing the incidence of renal tumours through exacerbation of spontaneous CPN

Nephropathy was reported in almost all the rats in the carcinogenicity study, including the controls. CPN is a common finding in aged F344 rats, with the incidence tending to be higher in males than females (Hard & Khan, 2004). Unfortunately, there were no female rats with which to compare the incidence of adenoma and nephropathy, although nephropathy was reported only in male rats, not females, in a 90-day gavage study (section 7.9.4). CPN in rats does not have a counterpart in humans. Chemically-exacerbated CPN has been linked to increased likelihood of developing renal tubule adenomas in rats, but to dismiss the human relevance of tumours on this basis, Hard & Khan (2004) propose that certain criteria should be met, which are explored below. Based on the histopathology of the kidneys and proliferative lesions, Lock & Hard (2004) placed hydroquinone (see above) in this category.

Severity of CPN

'The chemical must have been shown to exacerbate CPN to very advanced stages of severity, especially end-stage kidney, in comparison with control rats in a two-year carcinogenicity study'

Hard & Khan (2004) viewed this criterion to be one of the most important considerations, based on their own experience and that of other investigators (Eustis *et al.*, 1994; Seely *et al.*, 2002).

The severity of CPN is traditionally scored on a scale of 0 to 4 by estimating the percentage of parenchyma affected by CPN. The scale values 1 to 4 represent *minimal*, *mild*, *moderate* and *marked* states of CPN progression. Hard & Khan (2004) recommended a nine-point scale in the scoring of CPN severity. This proposed scale is based semi-quantitatively on disease progression: 0 is *no lesions*, 1 represents a *minimal* grade (≤ 5 lesions per both sections), 2 *mild* (6-15 lesions), 3 *low-moderate* (16-30 lesions), 4 *mid-moderate* (30-60 lesions), 5 *high-moderate* (focal lesions/casts too numerous to count), 6 *low-severe*, 7 *high-severe* and 8 *end-stage*. The grades from minimal to high-moderate represent a progressive increase in the number of CPN lesions as focal changes; low-severe represents the point where foci begin to coalesce into areas of cortical tubule change; high-severe where a majority of the cortical parenchyma is affected by CPN change; and end-stage where no, or almost no, normal parenchyma remains.

In the NTP *m-/p*-cresol carcinogenicity study, in which lesions were scored against the conventional system of 0 to 4, virtually all animals were affected by nephropathy at the end of the study, with the severity ranging from 1.4 in the control and low-dose groups to 2.1 in the high-dose group; a dose-related increase in severity, albeit slight, was thus shown. The study authors concluded that the nephropathy was microscopically typical of CPN, with various degrees of degeneration, regeneration and atrophy of the tubular epithelium; hyaline tubular casts; glomerulosclerosis; and interstitial fibrosis. The use of semi-quantitative considerations in the system proposed by Hard and Khan makes it

difficult to compare the two grading systems, although the description of the lesions in the NTP carcinogenicity report gives no indication that the lesions would be regarded as high-severe or end-stage. Taking into account the differences in how lesions are scored in the two grading systems, it has been proposed that a grade of 1 in the conventional system would translate to grades 1 to 4 (up to mid-moderate) in the expanded system (Travlos *et al.*, 2011). The incidence of adenomas in end-stage CPN has been reported to be around 10%, in contrast to an overall spontaneous rate of approximately 1% (Hard *et al.*, 2012).

The only other study in which nephropathy was observed was the 90-day rat gavage study (section 7.9.4.), in which the incidence was statistically significantly increased in the low- and high-dose male groups, but not the mid-dose group (there were no cases in any of the female rats). Furthermore, as the severity of the lesion was not increased by *p*-cresol exposure, the relationship to treatment of this finding in the 90-day study is debatable. Nephropathy was not detected in any other 90-day study. Following a re-evaluation of slides from 43 NTP 90-day studies with the extended grading scheme, it was reported that exacerbation of CPN at 90 days is a sensitive and specific indicator of increased renal tubule adenomas at two years (Travlos *et al.*, 2011). Conversely, the NTP had not reported or scored CPN as a diagnosis in the re-evaluated studies, a fact attributed by the authors to the different methods of severity scoring used; the extended system was stated to be more suitable for the elucidation of subtle effects and the detection of statistical differences and thus provided a more sensitive method.

The calorie and protein content of the diet have been proposed as influencing factors in the incidence and severity of CPN (Hard & Khan, 2004; Travlos *et al.*, 2011). The concern over this possible confounding factor in the interpretation of chronic rat studies was such that, in 1994, the NTP began to use a new diet, designated NIH-2000, that was lower in protein (14%) and higher in fibre and fat than the NIH-07 diet that had been in use since 1980 (protein content 24%). The NIH-2000 diet was used in the *m-/p*-cresol carcinogenicity studies, which makes it somewhat surprising that the incidence of nephropathy was so high in all the groups, including the controls, and complicates the interpretation of the CPN being exacerbated by treatment. Subsequent analysis of the incidence and severity of CPN in rats fed the two diets has demonstrated, however, that, whilst the incidence of early lesions was 100% in male rats in all the 90-day studies evaluated (half with the 'old' diet, half with the 'new'), the severity grade was greater in control rats given the NIH-07 diet than those fed the NTP-2000 diet (Travlos *et al.*, 2011). The NIH-07 diet was fed in the sub-acute and sub-chronic NTP studies reported in section 7.9.4. The 90-day gavage study used a different diet, but one with a comparable level of protein (23%). Comparison of the lesion severity between the 90-day gavage study and the two-year carcinogenicity study is therefore confounded by the different diets (and also the different laboratories undertaking the studies). Nevertheless, based on the scores of mainly minimal lesions in the 90-day study (all groups) and 2.1 (mild) in the high-dose group of the carcinogenicity study, *m-/p*-cresol did seem to slightly increase the severity both compared with the two-year control animals and with the high-dose group exposed for 90 days.

Increase in renal tubule tumours

'The tumours should occur in very low incidence'

A total of four renal tubule adenomas in four animals were revealed by the standard and extended pathology evaluations, all of which were in the high-dose groups; no tumours occurred in any other group. The incidence (8%) was not statistically significantly increased by a pairwise comparison with the control group, although it was higher than the concurrent historical control data (mean 0.3%, range 0 – 2%).

No other treatment-related tumours were induced in rats. Renal tumours did not occur in female mice, nor did the mice develop any other tumours of human relevance.

Histopathology of tumours

'The tumours should, in the most part, be minimal grade lesions conforming to small adenomas or lesions borderline between atypical tubule hyperplasia and adenoma'

The authors of the rat carcinogenicity study reported that all the renal tubule adenomas were small lesions, being approximately 0.5 mm in diameter. They were well circumscribed, discrete, round or oval masses greater than five times the diameter of a normal renal tubule. There was no evidence of progression of benign tumours to adenocarcinomas.

Location of tumours

'The tumours and any precursor foci of atypical hyperplasia must be restricted to CPN-affected parenchyma and are usually observed only towards the end of the two-year studies'

Renal tubule adenomas were first recorded at 725 days, i.e., at the end of the study; thus none of the animals that died early demonstrated this lesion.

ATH is an obligate precursor of renal tubule tumours; advanced stages of CPN represent a risk for the development of a low incidence of renal tubule tumours and ATH in F344 rats (Hard *et al.*, 2012). In a re-evaluation of slides from 24 NTP carcinogenicity studies, the occurrence of foci of ATH and adenoma was strongly associated with the two most severe grades of CPN (7 and 8 in the extended system), and especially with end-stage disease (stage 8) (Hard *et al.*, 2012). In contrast, Hard *et al.* (2012) failed to find any of these lesions (ATH and adenoma) in control male rats with severity grades of 0-5. In the m-/p- cresol rat carcinogenicity study, a dose-related increase in ATH was not observed. The study report does not provide information on the tissue localisation of the tumours.

Other microscopic findings

'Microscopic examination of renal parenchyma not involved in the CPN process should reveal no evidence of compound-induced cellular injury or other changes that would suggest alternative modes of action'

Apart from the nephropathy reported in the 90-day gavage and carcinogenicity studies, no renal lesions occurred in rats. The only renal lesion reported in mice was necrosis in high-dose animals (> 1400 mg/kg/d), all of which died early because of excessive toxicity.

The comparison of the kidney tumour findings in male rats exposed to *m-/p*-cresol with the criteria for assigning adenomas to chemically-exacerbated CPN are summarised in the table below.

Table 15. Comparison of the kidney findings in the *m-/p*-cresol carcinogenicity studies with the criteria for chemical exacerbation of CPN

Criterion	Comparison with criterion
Exacerbation of CPN to very advanced stages of severity (especially end-stage CPN) at doses associated with tumour increase, in comparison to control rats in a two-year carcinogenicity study.	Severity of nepropathy increased slightly in the high-dose group compared with controls and low-dose group, but did not appear to meet the severity classification of severe or end-stage. Comparison of CPN severity between 90-day gavage study and two-year carcinogenicity study difficult because of different diets employed. Overall, no evidence of chemically-

	exacerbated CPN in the 90-day rat studies. *Inconclusive – interpretation complicated by differences in lesion scoring systems and sensitivity thereof*
Slight increase in renal tubule tumours.	Four tumours in high-dose group (4/50 male animals), not statistically significant although above concurrent historical control range for male F344 rats; some of the historical control data derives from standard (less sensitive) histopathology evaluation. No renal tumours in female mice. *Met*
Tumours are usually adenomas which are often small size or borderline with atypical tubule hyperplasia.	Only adenomas were recorded, which were reported to be small in size. There was no evidence of progression to malignancy. *Met*
Tumours and any precursor foci of atypical hyperplasia must be restricted to CPN-affected parenchyma; and are usually observed only towards the end of the 2-year studies.	No information on whether the tumours were within areas of CPN; a dose-related increase in ATH was not observed. *Inconclusive* The first tumours were recorded at the end of the study. *Met*
Careful microscopic examination of renal parenchyma not involved in the CPN process should reveal no evidence of substance-induced cellular injury or other changes that would suggest alternative modes of action.	The only renal lesion reported in rats was nephropathy. Renal necrosis was reported in one study in mice, but only at excessively toxic doses. *Met*

Category 7. Chemicals increasing the incidence of renal tumours through an unknown mechanism, but which also exacerabate CPN

Chemicals were placed in this category if they increased both the incidence of renal tubule tumours and the incidence and/or severity of CPN, but for which there were no data to identify a mode of action underlying the tumour development that would permit them to be assigned to one of the preceding categories. Most of the chemicals also resulted in increased tubule hyperplasia. For *m-/p*-cresol, see the discussion on CPN exacerbation above.

Category 8. Chemicals increasing the incidence of renal tumours through an unknown mechanism but which do not exacerabate CPN

This category includes chemicals that increase the incidence of renal tubule hyperplasia and produce a statistically significant increase in renal tubule tumours in male rats without affecting the incidence or severity of CPN. Because of the absence of any data on mode of action, these chemicals cannot be assigned to any of the previous categories. In

the case of *m-/p*-cresol, the increase in renal tumours was not statistically significant, but there was a slight increase in the severity of CPN.

Category 9. Chemicals associated with a not statistically significant increase in the incidence of renal tumours in rats

In the *m-/p*-cresol rat carcinogenicity study (NTP, 2008) the increase in renal tubule tumours in the high-dose group (720 mg/kg/d *m-/p*-cresol mixture) was just outside statistical significance (p = 0.54 by pairwise comparison with the controls). It was outside the concurrent historical control range. Histopathology evaluations of the kidneys in the historical control studies were largely conducted by standard sectioning; the eMSCA notes that, in one historical study in which extended evaluations were performed, renal tubule adenomas were detected in 3/50 control female rats. A larger database of historical control data, comprising 69 NTP studies conducted between 1977 and 2004, gave an incidence of this tumour of 0.98% (range 0 – 6%) in male F344 rats, based on standard histology sections. When 13 NTP studies conducted before 1994 in male F344 rats were re-evaluated with extended histopathology, the incidence of renal tubule tumours increased from a mean of 0.62% (range of 0 – 2%) to a mean of 4.47% (range 0 – 16%) (Eustis *et al.*, 1994); the latter range therefore clearly exceeds the incidence in the *m-/p*-cresol study. However, the data are not directly comparable because these studies were performed many years before the cresol study, which was published in 2008.

Eleven of the 69 chemicals reviewed by Lock & Hard (2004) were associated with a small increase in renal tubule tumour incidence that was not statistically significant. In some cases, they also produced an increased incidence of renal tubule hyperplasia and/or an increased severity of CPN. In other cases, the authors stated that there was a very strong possibility that some of the tumour incidences would represent spontaneous occurrences and not be treatment related.

Four of the eleven reviewed chemicals had the same pattern of findings as *m-/p*-cresol: renal tumours in male rats only, no increase in renal tubule hyperplasia, no increase in CPN incidence, with or without an increase in CPN severity. Of these, one chemical (geranyl acetate) showed renal tubule adenomas (4%) only in the mid-dose group and together with moderate CPN (NTP concluded *'negative evidence of carcinogenic activity'*). Another (cinnamyl anthranilate) had a renal tumour incidence of 8% in the high-dose group, comprising two adenomas and two carcinomas, without an increased severity of CPN but with a dose-related mineralisation of the kidney (*'some evidence of carcinogenic activity'*). In a study with triethanolamine, the renal tumour incidence was 2%, 4%, 12% and 8% in the control, low-, mid- and high-dose groups, respectively (p = 0.053 for the mid-dose group). CPN severity was not increased in the treatment groups. Sub-chronic oral administration of triethanolamine resulted in histopathological changes in the proximal tubules in rats. The NTP classified this chemical as showing *'equivocal evidence of carcinogenic activity'* in male rats. Male rats exposed to tetrahydrofuran showed a dose-related increase in renal tubule tumours of up to 10% in the high-dose group (comprising three adenomas and two carcinomas) compared with 2% in the controls (one adenoma). The severity of CPN was not affected. The NTP concluded that this chemical showed *'some evidence of carcinogenic activity'* in male rats.

Category 10. Chemicals that produce an increase in renal tumours in mice but not in rats

This category is not applicable to *m-/p*-cresol.

A comparison of the available information on *m-/p*-cresol with the above categories indicates that the mixture best fits with category 9 (not statistically significant increase in renal tumours), but could also possibly be placed in category 6 (exacerbation of CPN).

In support of placing the substance in category 6, the increased incidence of renal tubule tumours was small, histopathologically the adenomas met the required criteria and were observed only at the end of the study, and there was no evidence of other renal injury. However, the criterion that is considered by experts in the field to be the most important, the exacerbation of CPN to severe or end-stage, did not appear to be met. There was also no robust evidence from the sub-chronic studies that there was a treatment-related increase in either incidence or severity of CPN. From an evaluation of the sub-chronic and carcinogencity data in male F344 rats of 24 chemicals tested by the NTP (Travlos *et al.*, 2011), it was concluded that chemical exacerbation of CPN severity at 90 days demonstrated a 100% sensitivity for predicting renal tubule tumours in the two-year studies (specificity 88%, based on 7 of the studies that reported such tumours at two years).

In an ealier investigation, also involving NTP studies (on 16 chemicals), that looked for biological predictors of a tumorigenic outcome, all the chemicals that produced kidney tumours in rats resulted in kidney weight increase (both absolute and relative to body weight) at 13 weeks (Boobis *et al.*, 2009). Overall, none of the exposure groups that had no effects in the kidney at 90 days had renal tumours after two years, whereas all exposure groups that had tumours after two years showed renal alterations (increased weight plus histopathology findings) at 90 days (Boobis *et al.*, 2009). In the 90-day studies evaluated in this report, an increase in relative kidney weight was recorded in male and female rats treated with *p*-cresol by gavage, which was explained by a decrease in the body weights. Exposure to *m-/p*-cresol resulted in slight but statistically significant increases in absolute and relative kidney weights in male rats and a decrease in absolute kidney weight in females, but without histopathology changes. Kidney weights were unaffected by exposure to *m-/p*-cresol in the mouse 90-day study. It was also noticeable that renal tubule hyperplasia was not increased by exposure to *m-/p*-cresol in the two-year rat study. Lock & Hard (2004) concluded that a definite background of foci of renal tubule hyperplasia was helpful in discriminating a spontaneous scenario from treatment-related effects, including chemical exacerbation of CPN; i.e., an increase in ATH reflects a chemically-associated renal tubule tumour response.

In further support of the adenomas not being attributable to chemical treatment, the increase in the high-dose group was slight and not statistically significant (although it is recognised that the *p* value was only just outside statistical significance). The incidence was higher than the concurrent historical control range (four studies plus the control group in the *m-/p*-cresol study), but in some cases there was a difference in the sectioning of tissues, with the most sensitive histopathology evaluation being conducted in the *m-/p*-cresol study. The incidence was well within a more extensive (but older) database of studies conducted in the same rat strain by the NTP.

Gut bacterial production of *p*-cresol has been implicated in the progression of chronic kidney disease in humans (for example, Chao & Chiang, 2015; Lau *et al.*, 2015). However, chronic kidney disease in humans is not comparable to CPN in rats. *p*-Cresol has not been reported to be a human renal carcinogen and did not promote the development of human bladder cancer (referred to by Cosmetic Ingredient Review (CIR) Expert Panel, 2006).

Overall, there are several pieces of evidence that support the conclusion that the renal tubule adenomas were spontaneous and not treatment-related. These are summarised below:

- the marginal increase in renal tubule adenomas was not statistically significant;
- the histopathology evaluation was more sensitive than in some of the historical control studies;

- the pattern of findings in 90-day studies did not match those reported to occur with renal carcinogens:
    - CPN severity was not increased in male rats;
    - absolute and kidney relative weights were not consistently increased in rats, in particular in the gavage study with doses up to 600 mg/kg/d *p*-cresol;
    - there were no treatment-related histopathology findings in the kidney in rats;
- in the two-year study, a dose-related increase in ATH did not occur;
- no other tumours in rats nor tumours of human relevance in mice were detected.

As noted above, calorie intake is an important factor in the development of CPN in male rats. A slight increase in food intake (and so calories) relative to body weight in the high-dose group (food intake comparable to controls but final body weight 15% lower) in the two-year study might have been responsible for the slight increase in CPN severity, which then led to a low level of spontaneous tumour formation in this group.

7.9.6.2. Conclusion on carcinogenicity

The NTP concluded that the rat carcinogenicity study provided equivocal evidence of a carcinogenic effect of *m-/p*-cresol. The NTP defines equivocal evidence as "*evidence of carcinogenic activity is demonstrated by studies that are interpreted as showing a marginal increase of neoplasms that may be chemical related.*"

The conclusion of the evaluation presented in this report is that the marginal increase in the incidence of renal tubule tumours was likely to be a consequence of spontaneous tumour formation. In particular, the absence of characteristic findings (absolute and relative kidney weight increases with histopathology changes in 90-day studies, increase of ATH in two-year studies, severe or end-stage CPN) that have been associated with chemically-induced renal tumours supports this position. Furthermore, the lack of statistical significance for the increased tumour incidence makes the evidence for the tumours being chemically induced rather weak. The increased incidence of squamous cell papilloma of the fore-stomach in mice was concluded to be treatment-related but, because of the different physiology of rodents and humans, is not relevant to humans.

The available rodent carcinogencity studies on *m-/p*-cresol therefore indicate that *p*-cresol does not present a carcinogenic hazard to humans. The concern for carcinogenicity has been clarified and no further information is required.

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

To inform on the concern that *p*-cresol was a suspected endocrine disruptor, this end-point was evaluated fully by the eMSCA.

7.9.7.1. Fertility

A two-generation study in rats was included in the registration dossier.

Table 16. Summary of two-generation reproduction study

Method	Dose levels	Results
Oral gavage in	0, 30, 175, 450	Observations comprised clinical signs, oestrous cyclicity, litter

corn oil Two-generation Rats, Sprague-Dawley, 25/sex/dose *p*-cresol (98.93% purity) GLP TSCA Health Effects Test Guideline for Specific Organ / Tissue Toxicity – Reproduction / Fertility Effects (EPA 1983) IUCLID 7.8.1 Reliability 1 Full study evaluated	mg/kg/d From 10/11 weeks pre-mating, 5d per week P0 and F1 females: 7 days per week through gestation and lactation	observations, post-mortem observations of parental animals and offspring, reproductive and offspring viability indices. ***Parental Toxicity*** *F0* At 450 mg/kg bw/d, 9/25 males (8 during 10-week pre-breed period & 1 during mating) & 8/25 females died (5 during 10-week pre-breed period, 2 during gestation, 1 during lactation). 1/25 female at 30 mg/kg/d was sacrificed in a moribund state during pre-breed period. Necropsy findings on animals that died before scheduled sacrifice: diffuse, focal or multifocal colour changes in the lungs; stained skin. Histopathology: congestion & haemorrhage of the lungs. Autolysis of seminal vesicles in 4/9 males. No treatment-related findings at necropsy & histopathology of animals that survived until the end of treatment. Overt clinical signs of toxicity: hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration at 450 mg/kg/d. Perioral wetness in both sexes at ≥ 175 mg/kg/d. Body weight: in males, decreased weeks 1-13 (↓ 12.7% at termination) at 450 mg/kg/d; in females, decreased in week 1 (5%) at 450 mg/kg/d & on lactation day 4 (5.8%). Body weight gain: at 450 mg/kg/d, decrease in males at weeks 0-1 (52%*), 3-6 (range 16-42%*) and 12-13 (46%*); decrease in females at weeks 0-1 (37%*), 8-9 (44%*) & days 0-4 of lactation (79%*). At 175 mg/kg/d, decrease in males at weeks 4-5 (13%*) & females at weeks 8-9 (35%*). Decreased food consumption in weeks 0-5 in males (range 7-25%*) and 0-1 in females (16%*) at 450 mg/kg/d. *F1* At 450 mg/kg/d, 6/25 males died (5 during pre-breed period, 1 during mating) & 10/25 females died (8 during pre-breed period, 1 during mating, 1 during lactation). An additional male death was attributed to dosing error, not toxicity. At 175 mg/kg/d, 1/25 males died (during mating). Necropsy and histopathology findings on animals that died before scheduled sacrifice: lung & skin findings as for the F0 parents. Additionally, congestion in the nasal turbinates & erythrocytes on skin surface in females. Reduced spermatozoa in the epididymides of 3/7 males. Autolysis of seminal vesicles in 3/7 males. Necropsy & histopathology of animals that survived until the end of treatment: 3/18 males with seminiferous tubule atrophy/degeneration and decrease in epididymal sperm numbers at 450 mg/kg/d; otherwise no treatment-related findings Overt clinical signs of toxicity: hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration at 450 mg/kg/d. Perioral wetness in both sexes at ≥ 175 mg/kg/d. Body weight: decreased weeks 1-13 in males (↓ 13% at termination) and weeks 0-4 in females (range 7-12%) at 450

mg/kg/d.

Body weight gain: 42%* decrease in males during weeks 0-1 at 450 mg/kg/d. Food consumption decreased in weeks 0-2 (24 & 9%*), 4-5 (6%*) and 6-10 (range 6-8%*) in males; 0-1 (16%*) and 4-5 (10%*) in females, all at 450 mg/kg/d.

Reproductive toxicity

No effects on oestrous cyclicity, gestation duration or sperm parameters at any dose.

The following reproductive parameters were recorded:

mg/kg bw/d	**0**	**30**	**175**	**450**
F0 parents				
No. of mated females	25	24	25	20
No. pregnant	23	23	24	17
No. live litters on post-natal day 0	23	23	24	16
Mating index % (males)	96.0	100.0	92.0	100.0
Mating index % (females)	100.0	100.0	100.0	100.0
Fertility index % (males)	95.8	95.8	95.7	82.4
Fertility index % (females)	92.0	95.8	96.0	85.0
Gestational index %	100.0	100.0	100.0	94.1
F1 parents				
No. of mated females	25	25	25	17
No. pregnant	23	23	19	13
No. live litters on post-natal day 0	23	23	19	13
Mating index % (males)	84.0	92.0	88.0	70.6
Mating index % (females)	96.0	100.0	96.0	94.1
Fertility index % (males)	95.2	95.6	86.4	75.0
Fertility index % (females)	95.8	92.0	79.2	81.3
Gestational index %	100.0	100.0	100.0	100.0

Offspring toxicity

There were inconsistent reductions in the live birth index and increase in the number of still-births in some groups:

mg/kg/d	**0**	**30**	**175**	**450**
F1 pups from F0 parents				
Live birth index %	99.3	98.6	95.8	96.9
No. of still births	2/292	4/290	13/312*	6/193
F2 pups from F1 parents				
Live birth index %	100.0	97.8*	98.5	94.5*
No. of still births	0/318	7/307*	4/265	9/163*

		No effects on post-natal survival indices at any dose level in F1 or F2. Body weight and sexual maturation in offspring not affected in any dose group in either generation. Parental toxicity NOAEL= 30 mg/kg bw/d (based on clinical findings and death of one male at 175 mg/kg bw/d) Offspring NOAEL= 175 mg/kg bw/d (based on decrease in F2 live birth index at 450 mg/kg bw/d) Reproductive NOAEL= 450 mg/kg bw/d (no indication of specific fertility effects at highest dose)

* Statistically significant, $p \leq 0.05$

In a two-generation study in which *p*-cresol was administered at doses up to 450 mg/kg/d, the only adverse effects on reproduction parameters were noted in slight reductions in the fertility index of males and females and the gestational index (F0 only) in the high-dose group, none of which was statistically significant. The severe toxicity observed at 450 mg/kg/d, including the death of several animals, compounded some of these parameters. For example, some males died during the mating period, before impregnation of the female with which they were paired; thus the male fertility index in these groups was reduced. Moreover, in the group in which a slightly reduced gestational index[12] was recorded, one of the pregnant females, and hence her litter, died during gestation. (A further female of this group died on gestation day 6, but was not included in the calculation of fertility and gestational indices as the pregnancy status was not confirmed by uterine staining.)

There was some evidence of offspring toxicity, in that the live-birth index and number of still-born pups were slightly but statistically significantly affected in the low- and high-dose groups of the F2 generation, but not in the mid-dose group. In the F1 generation, the increase in the number of still-births was only statistically significant in the mid-dose group, and the consequent decrease in the live-birth index of this group was not statistically significant. As these changes were inconsistent and small, the eMSCA does not consider that they provide evidence of reproductive toxicity.

There was no indication that *p*-cresol had a specific adverse effect on the reproductive organs in males or females. In the animals that survived until the end of treatment, the testes, epididymides, seminal vesicles, uterus and ovaries were normal in both generations, apart from a small number of high-dose F1 males (3/18) that had seminiferous tubule atrophy/degeneration and reduced numbers of epididymal sperm). In the animals that died early in the 450 mg/kg/d group, the testes, epididymides, uterus and ovaries were also normal, apart from reduced spermatozoa in the epididymides of 3/7 animals (F1 only). The seminal vesicles showed autolysis in 4/9 of the prematurely-deceased animals in the F0 generation and 3/7 in the F1 generation; the autolysis was likely to have occurred post-mortem. The increased oestrus cycle length that was reported in a 90-day study with *m-/p*-cresol mixture (section 7.9.4.1) was not reproduced in this study. *p*-Cresol did not affect pup weight nor indicators of sexual maturation at any dose in either generation.

[12] Gestational index = (number of females with live litters / number of females pregnant) x 100

Overall, the eMSCA does not consider that the slight changes in some of the parameters in this study, which occurred together with excessive parental toxicity, provide evidence of a specific effect on reproduction.

During its literature search, the eMSCA identified a two-page summary of an investigation in CD-1 mice that used the 'reproductive assessment by continuous breeding' protocol (Heindel *et al.*, 1997). This study used an *m-/p*-cresol mixture (ratio of each not stated) in concentrations of 0.25, 1.0 and 1.5% in feed (approximately 370, 1500 and 2100 mg/kg/d). The details are scant, but even at the extremely high dose of 2100 mg/kg/d, the authors concluded that *m-/p*-cresol did not demonstrate selective reproductive toxicity nor toxicity to the reproductive organs and tissues (including sperm parameters).

7.9.7.2. Developmental toxicity

The registration dossier included developmental toxicity studies in rats and rabbits.

Table 17. Summary of developmental toxicity studies

Method	Dose levels	Results
Oral gavage in corn oil Rats, Sprague Dawley, female 25/group for test material and 50 control females *p*-cresol (purity 98.93%) GLP TSCA Health Effects Test guidelines for Specific Organ / Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987) IUCLID 7.8.2 Reliability 1 Full study report evaluated	0, 30, 175, 450 mg/kg bw on days 6-15 of gestation All animals sacrificed on gestation day 21	Dams evaluated for body weight, liver and gravid uterine weight, number of corpora lutea and number and status of implantation sites. All foetuses were counted, sexed, weighed and examined for external malformations and variations. Half the foetuses were examined for visceral malformations, variations and soft tissue craniofacial malformations. The remainder were examined for skeletal malformations and variations. ***Maternal toxicity*** At 450 mg/kg bw/d, 3/25 females died; two further dams at this dose were removed from the study because of a dosing error. No dams aborted or delivered early. Clinical signs(450 mg/kg/d only) included ataxia, hypoactivity, twitches, tremors, prone, laboured, audible respiration, gasping, perioral wetness, peri-nasal encrustation, and red fluid expelled from mouth. At 450 mg/kg/d, maternal body weight reduced when measured on day 11 (by 11%*) and day 15 (by 7.2%*). Overall corrected body weight change reduced by 40%* compared with controls. Food consumption over days 6-15 was 24%* lower than controls. No treatment-related gross lesions. Relative but not absolute liver weight increased by 5%* at 450 mg/kg/d. ***Developmental toxicity*** The following gestational parameters were unaffected by treatment: number of corpora lutea, number of total, non-live or live implants, sex ratio. Foetal body weights / litter reduced at 450 mg/kg/d (6%*). No treatment-related differences in any individual external or visceral variation, pooled visceral or skeletal variation or for total variations. Some individual skeletal variations showed

<table>
<tr>
<td></td>
<td></td>
<td>different incidences compared with the control group, but some of these were reduced incidences or findings that did not occur in a dose-related manner. The following findings were considered to be treatment-related:

<table>
<tr><th>mg/kg bw/d</th><th>0.0</th><th>30.0</th><th>175.0</th><th>450.0</th></tr>
<tr><td>No. of foetuses / litters</td><td>305 / 45</td><td>136 / 21</td><td>131 / 21</td><td>126 / 17</td></tr>
<tr><td>No. bi-lobed cervical #6 centrum
Foetus
Litter</td><td>
7
(2.3%)
5</td><td>

2
2</td><td>

2
1</td><td>

9 (7%)*
7</td></tr>
<tr><td>Reduced no. of caudal segments
Foetus
Litter</td><td>
37
(12%)
16</td><td>

17
8</td><td>

8
4</td><td>

32
(25%)
12*</td></tr>
<tr><td>Unossified #5 sternebrae
Foetus
Litter</td><td>

6 (2%)
4</td><td>

1
1</td><td>

0
0</td><td>

11
(9%)*
6</td></tr>
</table>

Isolated incidences of ecchymosis (head, extremities, trunk) in all groups without a dose-response relationship.

Maternal NOAEL= 175 mg/kg bw/d based on deaths, clinical signs of toxicity and decreased body weight and food consumption at 450 mg/kg/d.

Developmental NOAEL= 175 mg/kg bw/d based on increased incidence of skeletal variations at 450 mg/kg/d.</td>
</tr>
<tr>
<td>Oral gavage in corn oil

Rabbits, New Zealand white, 14/test group and 28 controls

p-cresol (purity 98.93%)

GLP

TSCA Health Effects Test guidelines for Specific Organ / Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)

IUCLID 7.8.2
Reliability 1
Full study</td>
<td>0, 5, 50, 100 mg/kg bw on days 6-18 of gestation

All animals sacrificed on gd29</td>
<td>Dams evaluated for clinical signs, food consumption, body weight, liver weight, gravid uterine weight, number of corpora lutea, number and status of implantation sites. Stomach, liver, gall bladder, kidneys and uterus examined by necropsy.

All foetuses counted, sexed, weighed, examined for visceral and skeletal malformations and variations. Approximately half examined for soft tissue craniofacial malformations.

Maternal effects

Dams died at 100 mg/kg bw/d (5/14) and 50 mg/kg bw/d (2/14).

No statistically significant changes in body weight or body weight gain in any dosed group compared with controls, nor in food consumption. No change in absolute or relative liver weight.

Clinical signs at 100 and 50 mg/kg bw/d included hypoactivity, gasping, cyanosis, laboured, rapid, audible respiration and ocular discharge.

Developmental toxicity

The following gestational parameters were unaffected by treatment: number of corpora lutea, number of total, non-live or live implants, sex ratio, foetal body weights per litter.</td>
</tr>
</table>

report evaluated		No treatment-related differences in individual external malformations / variations, malformations / variations by category or total malformations / variations. Ecchymosis of the head in 0/193, 2/93 (2.2%), 2/80 (2.5%) and 2/40 (5%) at 0, 5, 50, 100 mg/kg/d. Ecchymosis of extremities in one control; no occurrence on the trunk. Maternal NOAEL= 5 mg/kg bw/d based on deaths and clinical signs of toxicity at 50 mg/kg/d. Developmental NOAEL= 100 mg/kg bw/d based on no adverse developmental effects at the highest dose tested.

* Statistically significant, $p \leq 0.05$

In a rat developmental toxicity study, *p*-cresol administered at doses up to 450 mg/kg/d by gavage on days 6-15 of gestation resulted in severe maternal toxicity at the top dose (deaths, decreased food consumption and body weight, clinical signs of toxicity). Foetal toxicity at this dose manifested as a decrease in foetal weight (6%) and an increase in the incidence of some skeletal variations. The eMSCA considers these effects to be secondary to maternal toxicity and/or non-specific offspring toxicity and not indicative of a specific effect on development. Gestational parameters were not affected at any dose.

In a developmental toxicity study in rabbits, *p*-cresol was also administered at doses that resulted in maternal deaths and clinical signs (at 50 and 100 mg/kg/d). There was no parental toxicity at the lowest dose of 5 mg/kg/d. The only foetal effect that occurred with a dose-response relationship was ecchymosis (bruising / blood spot) of the head, which, however, was not statistically significant at any dose. This finding was recorded as a variation by the study authors. Ecchymosis of other parts of the rabbit body and of the rat (head, extremities, trunk) occurred only in isolated animals of all groups, including the controls. Given that the incidences of this variation were very low and inconsistent across studies and groups, the eMSCA considers it to be a chance finding.

7.9.7.3. Summary and discussion of reproductive toxicity

In both the two-generation study and the developmental toxicity studies, *p*-cresol was administered at doses that resulted in the deaths of adult animals and other indications of parental toxicity. In spite of the consistent and severe parental toxicity, there were no indications that the substance elicited a specific effect on fertility or developmental toxicity.

Therefore, the available, well-conducted two-generation and developmental toxicity studies with *p*-cresol administered to rats and rabbits provide sufficient information for the eMSCA to conclude that the registered substance does not have a specific effect on reproductive toxicity.

7.9.8. Medical surveillance data

The registration dossier includes a report of medical investigations performed on workers from two production plants that manufacture *o*-, *m*- and *p*-cresol. Data from about 100 workers per year over a period of 15 years (1997-2001) were evaluated. The annual examinations included medical history, physical examination, lung function, ECG/ergometry, vision testing, audiometry, laboratory examinations of blood and urine and biomonitoring. Additional, specific examinations relevant to possible cresol exposure included physical examination of the lung, mouth and nose and lung function tests.

Biomonitoring results in urine confirmed that workers were exposed to cresols, in all cases below the BLW value (Biologischer Leitwert) of 200 mg/L urine. No health effects

such as irritation of the skin, mucosa membranes or upper respiratory tract attributable to cresol exposure were detected.

7.9.9. Hazard assessment of physico-chemical properties

Not assessed

7.9.10. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The primary expression of toxicity is local irritancy or corrosivity. As studies that could have explored repeated-exposure site-of-contact effects are lacking, the eMSCA has taken a qualitative approach to the risk characterisation. *p*-Cresol is considered to have moderate hazard because of its acute toxicity (attracting classification with H301 and H311) and its corrosivity (attracting classification with H314). The IR & CSA Guidance, Part E, table E.1 indicates that for such substances, measures should be in place to limit release using containment or exhaust ventilation as appropriate.

7.9.11. Conclusions of the human health hazard assessment and related classification and labelling

p-Cresol has a harmonised classification on Annex VI of Regulation (EC) 1272/2008 for acute oral toxicity category 3 (H301), acute dermal toxicity category 3 (H311) and skin corrosion category 1B (H314). The information in the registration dossier indicates that it is not a skin sensitiser.

Repeated-dose studies via the oral route on *p*-cresol and a 60:40 mixture of *m-/p*-cresol have been reported in the registration dossier. Some additional information on oral administration was identified by the eMSCA.

In repeated-dose toxicity studies in rats and mice, the principal finding was lesions that were consistent with irritation in the nasal cavity and respiratory tract. This may have been attributable to inhalation of dust from the diet, although this is unconfirmed. A similiar finding, epithelial metaplasia of the trachea in the rat gavage 90-day study, might also have been a local effect. The 28-day study of m-/p-cresol in mice showed lung effects, in the form of bronchiolar epithelial hyperplasia, which would not be expected to be the result of inhaling a dust from the diet. A similar finding was reported in the mouse carcinogenicity study (see section 7.9.6), also with the m-/p- mixture. The authors of the carcinogenicity study postulated that p-cresol vapour from the feed was responsible for the nasal and bronchiolar effects, although the eMSCA notes that p-cresol has a relatively low vapour pressure. The low odour threshold of p-cresol (see section 7.12.1), however, indicates that the substance does volatilise. Overall, the eMSCA concludes that the lung effects in mice after oral administration were a local rather than systemic effect. In hamsters, an increased incidence of mild and moderate fore-stomach hyperplasia was reported following dietary exposure; such effects with irritant/corrosive substances can normally be attributed to retention of the substance in the fore-stomach.

Absolute and/or relative kidney weights were reduced in all but the 90-day study in mice with *m-/p*-cresol mixture; however, the only histopathology finding was an increased incidence of nephropathy in all the male dose groups in the gavage 90-day study with *p*-cresol. There was not a clear dose-response relationship in the incidence or severity of the nephropathy, with the lesions being largely scored as minimal. Furthermore, nephropathy was recorded in 20% of animals of the control group. Therefore, this isolated finding in one study is not considered to provide evidence of a treatment-related effect. In some studies the kidney weight changes occurred at doses below those that caused reduced body weight.

Liver weight was also consistently increased; this was without histopathology correlates in rats, but a small number of mice dosed with 30 000 ppm *p*-cresol in the 28-day study

(all of which died early in this dose group) showed some liver lesions. Transiently elevated serum enzymes, elevated total bile acids and decreased 5'-nucleotidase in the 90-day study with *m-/p*-cresol provided some evidence of hepatocellular injury, but the urinalysis results did not support hepatic injury.

The NOAEL and LOAEL values from the available rat and mouse 28-day and 90-day repeated-dose toxicity studies did not highlight a noticeable difference in the potency of the individual *p*-isomer or the *m-/p-* mixture. Moreover, the lead effects were comparable, with the effects mainly being local effects on the nasal tissues together with some liver and kidney weight changes. Two effects were reported with the mixture but not with *p*-cresol alone: increased colloid in follicular cells of the thyroid gland and an increase in oestrus cycle length, both in rats.

The genotoxic potential of *p*-cresol has been investigated in *in* vitro and *in vivo* tests. *p*-Cresol was positive in an *in vitro* chromosome aberration assay in Chinese hamster ovary cells both with and without metabolic activation. It did not show evidence of mutagenicity in bacterial or mammalian cells *in vitro*. The potential to induce clastogenicity *in vivo* was investigated in a micronucleus test in mice, in which the frequency of micronuclei in the peripheral blood was determined after 13 weeks of administration of *m-/p*-cresol mixture. The micronucleus test was negative at the maximum dose tested of *m-/p*-cresol mixture (1693 mg/kg/d), which equates to 667 mg/kg/d *p*-cresol. This test was sufficient to negate concerns from the *in vitro* chromosomal aberration assay. *p*-Cresol was not a germ cell mutagen under the conditions of the available dominant lethal test. Overall, the eMSCA concludes that *p*-cresol is not genotoxic *in vivo*.

The carcinogenic potential of *m-/p*-cresol 60:40 has been investigated in two-year studies in male rats and female mice. In male rats, a low incidence of renal tubule adenomas in the high-dose group was reported, which was not statistically-significant. Taking into account the low incidence and absence of characteristic findings associated with chemically-induced renal tubule tumours, it was concluded that these tumours were most likely to be of spontaneous formation. In female mice, the only notable findings was a statistically significant increase in the incidence of squamous cell papilloma of the fore-stomach. This was concluded to be treatment related; however, because of differences in the physiology of rodents compared with humans (the fore-stomach of rodents not having a counterpart in humans; also, the absence of a vomiting reflex in rodents), this finding was not relevant to humans. The overall conclusion was thus that the available rodent studies indicated that *p*-cresol does not present a carcinogenic hazard to humans.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not evaluated.

7.10.2. Endocrine disruption - Human health

Endocrine disruption was one of the concerns listed on the CoRAP and was thus within scope of the evaluation. The potential of *p*-cresol to be an endocrine disruptor in relation to human health only was evaluated.

As there is not currently an accepted EU definition of an endocrine disruptor for regulatory purposes, the information available on the endocrine disruption potential of *p*-cresol was compared with the World Health Organisation / International Programme on Chemical Safety definition (WHO / IPCS, 2002), which states that:

> *An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations.*

This definition is well established and widely recognised and has been produced by a global, authoritative organisation. It is supported by a number of organisations and regulatory bodies around the world, including the United States Environmental Protection Agency, the Canadian Centre for Occupational Health and Safety and the International Union of Pure and Applied Chemistry.

Justification for the inclusion of p-cresol on the CoRAP as a suspected endocrine disruptor

p-Cresol was included on the CoRAP as a suspected endocrine disruptor because of its listing in the TEDX list of potential endocrine disruptors.

The Endocrine Disruption Exchange (TEDX)[13] is a United States environmental organisation that purports to list chemicals with the potential to affect the endocrine system. The TEDX website does not provide a definition of endocrine disruptors by which it sets its criteria for inclusion of substances, but states that '*endocrine effects include not only direct effects on traditional endocrine glands, their hormones and receptors (such as estrogens, anti-androgens, and thyroid hormones), but also all other hormones and signaling cascades that affect the body's systems and processes, including reproductive function and fetal development, the nervous system and behavior, the immune and metabolic systems, gene expression, the liver, bones, and many other organs, glands and tissues.*' The TEDX database presents the chemicals for which at least one peer-reviewed study that reports findings on one or more of the above has been published. In this respect, there are some obvious and fundamental differences from the approach to the identification of endocrine disruptors advocated by the WHO.

The TEDX database entry for *p*-cresol comprised four references to published literature (Kawakami *et al.*, 2009; Nakamura *et al.*, 1989; Nishihara *et al.*, 2000; Thompson *et al.*, 1994). Of these, only one (Nishihara *et al.*, 2000) provides some information on the endocrine activity of *p*-cresol. In this paper, which reported the screening of 517 chemicals in a yeast two-hybrid *in vitro* system, *p*-cresol was determined to be an oestrogenic agonist because it had a relative effective concentration[14] of greater than 10% of the agonist activity of 17β-estradiol, which was used as a standard. The eMSCA considers that the relevance of this *in vitro*, non-mammalian system, is limited for the purposes of determing if a substance meets the WHO definition of an endocrine disruptor.

Other available evidence to inform on the endocrine-disrupting potential of p-cresol

To determine if a substance meets the WHO definition of an endocrine disruptor, the most relevant data to consider for human health are those from studies on intact organisms and their progeny. Whole-animal data on *p*-cresol and a 60:40 mixture of *m*-/*p*-cresol that provide information on this mode of action are available for the end-points repeated-dose toxicity (rats and mice), carcinogenicity (rats and mice) and reproductive toxicity (rats and rabbits).

In the 28-day and 90-day studies in rats and mice, effects on brain and testes relative weights occurred only at high doses and were secondary to the general toxicity and decreased body weights at these doses. Occasional observations of uterus atrophy and one incidence of ovarian atrophy were secondary to the general toxicity, particularly the

[13] http://www.endocrinedisruption.org/endocrine-disruption/tedx-list-of-potential-endocrine-disruptors/overview (accessed 28th September 2015)

[14] 10% relative effective concentration (REC10) = the concentration of test chemical showing 10% of the agonist activity of 10^{-7} M 17ß-oestradiol, which is the optimum concentration for this substance. The study authors judged a chemical to be positive when the activity of the test substance was higher than REC10 within the concentration tested.

weight loss and hence poor nutrition, that occurred in these animals. There were no indications that the uterus, ovary and testes were specifically targeted by *p*-cresol.

There were no adverse findings in the thyroid gland in rats or mice from administration of pure *p*-cresol for 28 or 90 days. Increased colloid in follicular cells (minimal to mild) was observed in rats with the *m-/p*-cresol mixture, but in the absence of this finding with any of the pure isomers and without associated follicular cell hypertrophy or hyperplasia, the study authors concluded that it might have been secondary to decreased food consumption and body weights, since under-nutrition in rats has been associated with increased thyroid gland weights.

There were no biologically meaningful effects on reproductive end-points in male rats nor in male or female mice in 90-day studies with the *m-/p*-cresol mixture. In the rat study, an increased oestrus cycle length was noted in the mid- and high-dose groups. However, this finding was not reproduced in a two-generation study in rats with the *p*- isomer by itself. DECOS (1998) reports that women in the former Soviet Union who were engaged in the manufacture of enamel-insulated wires or tricresylphosphate and occupationally exposed to cresol (mixture of *o*-, *m*- and *p*-) and other substances, including chlorobenzene and phosphoryl chloride, had menstrual disorders, hormonal imbalances, increased frequency of perinatal mortality and increased abnormal development of newborns. However, DECOS noted that no data on exposure levels, exposure duration or employment duration, presence of other chemicals, or control groups were presented. The eMSCA therefore does not consider that this provides evidence of an endocrine disruption potential for *p*-cresol.

In a rat two-generation study conducted with *p*-cresol administered up to 450 mg/kg/d (a dose that was severely toxic to the parent animals), there were no effects on reproductive parameters or reproductive organs that were attributable to a specific toxic effect. Pup development and sexual maturation were normal at all doses. It was thus concluded that *p*-cresol does not adversely affect fertility or sexual function.

Two developmental studies were available in rats and rabbits. In both studies, *p*-cresol was administered at doses that resulted in maternal toxicity, including death. In neither study was there any evidence of a specific effect on gestational parameters nor on development (malformations, variations, survival of foetuses).

In the rat and mouse two-year carcinogenicity studies, there were no findings related to endocrine organs following chronic exposure to a mixture of *m-/p*-cresol and no endocrine-mediated tumours (section 7.9.6.).

The registrants provided additional information to support their conclusions that *p*-cresol is not an endocrine disruptor (IUCLID section 7.8.1). They reported that the EADB database (estrogenic activity database for assessing potential endocrine activity, produced by the US Food and Drug Administration in conjunction with other global bodies and institutions) contained two entries for *p*-cresol. The first of these was the yeast two-hybrid system already mentioned (Nishihara *et al.*, 2000), whilst the second was an oestrogen-receptor binding assay (Blair *et al.*, 2000) that the registrants concluded did not demonstrate oestrogenic activity for *p*-cresol. During a literature search, the UK CA identified another publication on oestrogen-receptor binding (Terasaka *et al.*, 2006). In this study, gene regulation by DNA microarray analysis was investigated in the breast cancer cell line, MCF-7, following exposure to 10 µM *p*-cresol for three days. *p*-Cresol did not show any oestrogenic activity in this assay. It was also not oestrogenic in a carp hepatocyte vitellogenin assay, but demonstrated some anti-oestrogenic activity (Letcher *et al.*, 2005). In the same study, aromatase (CYP 19) activity of human H295R adrenocortical carcinoma cells was not affected by incubation with *p*-cresol.

A screen of the OECD QSAR Toolbox (version 3.2.0.013) for *p*-cresol by the eMSCA was consistent with the outcomes in the registrants' report of the same (IUCLID section 7.8.1). According to the Toolbox, there was no relevant oestrogen-receptor binding

affinity reported in the OASIS database 9 (a commercial database of 1606 experimental oestrogen-receptor-binding affinities). Relative *in vitro* binding values for the human oestrogen receptor were reported to be 0%. The registrants also reported that, according to another database utilised by the Toolbox (yeast oestrogen assay, measure of relative gene activation, University of Tennessee-Knoxville, USA), *p*-cresol was inactive. In conclusion, QSAR analysis did not identify endocrine activity for *p*-cresol. In a search of two high-throughput *in vitro* screening systems by the registrants (ToxCast and Tox21, developed in cooperation with the US Environmental Protection Agency), of the 12 assays that were relevant for endocrine-related activities, one gave a questionable positive result with *p*-cresol, with the others being clearly negative.

The available data on the potential of *p*-cresol to be an endocrine disruptor for human health is summarised in the table below, in line with the OECD conceptual framework for the testing and assessment of endocrine disruptors OECD, 2012.

Table 18. Summary of the available information on the potential of *p*-cresol to be an endocrine disruptor for human health

Level 1 Non-test information	MW = 108.14. Vapour pressure = 14.66 Pa. Chemical reactivity indicated by harmonised classification for skin corrosion. Endocrine-like activity not indicated by OECD QSAR Toolbox analysis.
Level 2 *In vitro* assays providing data about selected endocrine mechanisms / pathways	Reported to be an oestrogen agonist in a yeast two-hybrid system Nishihara *et al.*, 2000. No oestrogenic activity in two oestrogen-receptor binding assays Blair *et al.*, 2000; Terasaka *et al.*, 2006. Anti-oestrogenic activity in a carp hepatocyte vitellogenin assay; no change to aromatase activity in a human cell line Letcher *et al.*, 2005. No concerns identified from high-throughput screening assays (ToxCast & Tox21).
Level 3 *In vivo* assays providing data about selected endocrine mechanisms / pathways	No available studies
Level 4 *In vivo* assays providing data on adverse effects on endocrine relevant endpoints	No evidence of specific toxicity to the brain, thyroid, testes, uterus or ovaries in 28-day and 90-day studies with *p*-cresol. Oestrus cycle lengthened in rats in one study with *m-/p*-cresol mixture but not reproduced in a two-generation study with *p*-cresol. No endocrine-related adverse effects in two-year carcinogenicity studies in rats and mice. No evidence of a specific effect on developmental toxicity in rats or rabbits in developmental toxicity studies.
Level 5 *In vivo* assays providing more comprehensive data on adverse effects on endocrine-relevant end-points over more extensive parts of the life cycle of the organism	No evidence of specific effects on fertility, sexual function, pup development or sexual maturation at doses that were severely toxic to parents in a two-generation study in rats.

Discussion of evidence for p-cresol being an endocrine disruptor for regulatory purposes

Endocrine disruption was identified as a potential concern for *p*-cresol during manual screening because of its inclusion on the TEDX database. This database is used as a means to capture information on substances for which at least one peer-reviewed study that reports findings on one or more end-points, not all of them clearly associated with functional effects on the endocrine system, has been published. As of June 2015, there were almost 1000 substances on the list. The inclusion of *p*-cresol was based on four publications, only one of which was directly related to potentially direct endocrine activity; in this, *p*-cresol was determined to be an oestrogenic agonist in an *in vitro* yeast two-hybrid system.

The available data to inform on *p*-cresol's endocrine disruption potential in intact organisms has been thoroughly evaluated by the eMSCA. Many *in vivo* studies at levels 4 and 5 of the OECD conceptual framework for the testing and assessment of endocrine disruptors (OECD, 2012) were assessed; in none of these was there a robust indication that *p*-cresol altered the function of the endocrine system in the investigated animals.

7.10.3. Conclusion on endocrine disrupting properties

Human health conclusion

To repeat the WHO definition, *'An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations.'*

There is a good-sized database on the mammalian toxicology of *p*-cresol in intact organisms, supported by studies on the 60:40 mixture of *m-/p*-cresol. These include 28-day and 90-day repeated-dose toxicity studies, a two-generation study, developmental toxicity and carcinogenicity studies. None of these provided robust evidence to suggest that *p*-cresol altered the function of the endocrine system and thus resulted in adverse effects in an intact organism or its progeny. The eMSCA concludes that *p*-cresol does not meet the WHO definition of an endocrine disruptor.

The concern has been clarified and no further information is requested.

7.11. PBT and VPVB assessment

Not evaluated

7.12. Exposure assessment

This exposure assessment discusses exposures arising from the uses covered in REACH registrations. It does not provide a comprehensive assessment of all potential sources of human exposure which will include exposure arising from intentional use and incidental exposure from natural sources.

Cresols are found in plant lipid fractions including many plant derived oils, they are formed in air due to photochemical reactions between toluene and photochemically generated hydroxyl radicals, they are generated when organic material is burned (e.g. forest fires) and they are present in volcanic emissions. Man-made incidental sources include coal and wood burning, municipal incinerators, vehicle emissions and cigarettes. Owing to its occurrence in plants, *p*-cresol is also present in foods and beverages such as tomatoes, ketchup, asparagus, cheeses, butter, bacon, smoked foods, red wine, raw and roasted coffee and black tea. Cresols are also produced during putrefaction and *p*-cresol is formed endogenously during the anerobic bacterial breakdown of amino acids in the

intestine (tyrosine metabolism). It is therefore a normal consitutent of human urine. The SIAR reported levels of excretion ranging from 16 – 74 mg *p*-cresol /24 hours[15].

All of these sources of exposure will contribute to the body burdens of workers at sites intentionally using *p*-cresol and those who may be exposed to trace amounts via articles. When considering the significance of exposures that arise from the uses covered in REACH registrations, it is important to set these into the context of the additional background exposure.

7.12.1. Human health

The exposure assessment submitted by the Registrants covers workers engaged in the manufacture and use of *p*-cresol at industrial sites and consumer exposure via service life of articles. The Registrants have not included scenarios covering professional exposure. Although professionals do not handle *p*-cresol, or process polymers containing *p*-cresol into articles, they will be exposed to the same articles that are handled by consumers and may have a higher level of exposure to articles than has been assumed for consumers, particularly if they are engaged in the maintenance or recycling of electrical articles. This will be considered further in section 7.12.1.2.

7.12.1.1 Worker

The worker exposure assessments for the inhalation route have been performed using combinations of modelled data (ECETOC TRA V2 and Stoffenmanager 3.5) or modelled (ECETOC TRA V3) and measured data. Dermal exposure has been assessed using the ECETOC TRA tool V2 or V3 in all cases. Although there appear to be some differences between Registrants in the way exposures are assessed, this seems to be due to the situation where Registrants update their dossiers at different times. It is not clear if this practice will result in differences in the information that communicated to downstream users for exposure scenarios that are common to all Registrants.

Note to Registrants: To ensure the reliability of information in the exposure scenarios that are communicated to downstream users, all registrants should ensure that they update their CSRs and exposure scenarios for downstream communication promptly when they receive new information. This evaluation report identifies new information that has been obtained. The eMSCA expects that all registrants will ensure that this is taken into account in their own exposure assessements.

The measured data used for the CSR was obtained from two reports. [redacted] provides information on exposures at two EU manufacturing sites and is discussed in more detail in the confidential annex. [redacted] summarises exposure values from the MEGA exposure database (693 data points from 60 industry branches and 138 working areas) which were obtained between 2000 and 2011 at downstream user premises in Germany to fulfil requirements of the German accident insurance institutions. Of the 693 samples, 127 were for cresols (all isomers), 228 were for o-cresol, 177 were for m-cresol and 161 were for *p*-cresol. The industries appearing most frequently in the data set include; iron and non-ferrous foundries, electrical engineering, plastics and rubber products manufacture, processing and treatment of metals, processing of liquid coating materials (surface treatment and hardening) and the processing and treating of wood. The work areas appearing most frequently in the data set include: foundries (core shop, moulding shop, casting area and fettling); surface coating (mechanical application and application with machines also boiler pressure impregnation); liquid paint coating

[15] http://www.inchem.org/documents/sids/sids/m-p-cresols.pdf

(paint preparation, paintshop and dipping/pouring of coating materials) and the manufacture of plastic sheets, tubes and profiles and semi finished plastic products. Since the data cover all cresol isomers and mixed cresols, the industry groups covered in the data set do not necessarily provide an accurate indication of industries that use specifically *p*-cresol. However, processes that are covered in the registration are visible in this data set.

From the information in the report, it is clear that these are routine measurements taken to check that controls are working as intended rather than to characterise worker exposure. The majority of the measurements were obtained using static sampling rather than personal sampling (62.2% vs 37.8%). The report provides summarised information about the use of mechanical ventilation and local exhaust ventilation (LEV) which suggests that mechanical ventilation and/or LEV was in place for at least half of the measurements, but it is not possible to link this information to specific industries, work areas or measurements.

The limit of quantification (LOQ) for the analytical method is reported as 0.5 mg/m^3 for a 40 L sample. According to the report, 85.9% of the measurements were obtained using sampling times of 1 hour or more and 98.7% of the samples were below the LOQ. The report did not provide information on the substances or quantities detected in samples that were above the LOQ. Where this report has been used by Registrants, it has been used to provide a value for 8-hr TWA exposure and a value of half the LOQ has been used. To provide a value for short-term peak exposure, the 90th percentile value from the short-term measurements reported by Allmenginger 2012 has been used.

When considering potential occupational exposure to *p*-cresol, it is also relevant to consider that *p*-cresol has a pungent odour. Odour thresholds ranging from 0.00005 – 0.03 mg/m^3 have been reported in various publications[16,17,18]. These concentrations are well below the LOQ for currently available routine monitoring methods. It is not clear where the irritant threshold lies in relation to odour thresholds. However, it seems reasonable to assume that in modern workplaces, to maintain an acceptable working environment, steps will be taken to limit the release of pungent substances into the working air. The fact that *p*-cresol appears generally not to be detected during routine monitoring is consistent with this assumption. It therefore seems reasonable to conclude that the information in [redacted] is indicative of the levels of full-shift inhalation exposure *p*-cresol that will occur at industrial sites handling *p*-cresol and polymers formulated with *p*-cresol. There is greater uncertainty about possible short-term peaks since these measurements are in the minority in the [redacted] dataset. Although the Registrants have taken the reasonable step of using the best source of measured data that is available, the eMSCA notes that this data was collected at manufacturing sites and it is not clear how representative the operating conditions (OCs) and risk management measures (RMMs) at manufacturing sites are for the range of downstream processes to which this 90th percentile value is being applied. This source of uncertainty will be considered further in relation to the downstream scenarios where this 90th percentile value has been applied.

Manufacture

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[16] EPA March 1992: Reference guide to Odour thresholds for hazardous air pollutants.

[17] Leonardos G, Kendall D, Barnard N (1969) Odour threshold determinants of 53 odourant chemicals. J Air Pollut Contr Assoc, 19, 991-995.

[18] Nagata y (2003) measurements of odour threshold by triangle odour bag method. Odour Measure, Rev 118-127.

Typically, *p*-cresol is manufactured in a mainly closed process in which chemical reactions take place at elevated temperatures. Opportunities for exposure potentially arise during sampling activities. Samples, which are likely to be at elevated temperatures (typically around 40°C), are collected into sealed vessels which are vented to LEV, minimising this potential source. Drum filling and tanker loading activities provide another potential opportunity for exposure. Drum filling is performed in an area separated from the main production areas fitted with spot extraction to minimise release and workers are required to wear chemical resistant gloves and close fitting goggles/face shields. Tanker filling is performed outdoors controlled from a panel at a distance from the filling point. However, workers need to approach tankers to connect and disconnect pipes and for this specific activity wear full face masks fitted with ABEK filters, chemical resistant gloves and suits. RPE is also required when changing the filters fitted to extraction systems.

The PROCs selected for this scenarios include PROCs 1, 2, 3, 8b, 9 and 15. Exposure values were obtained using the ECETOC TRA tool V3 or 3 or measured data. The RMMs identified include the use of LEV (effectiveness based on tool defaults) and gloves with an assumed effectiveness of 95% or 98% for transfers.

Inhalation exposure

With the exception of PROC 1 which was assessed using the ECETOC TRA model V3, inhalation exposures have been assessed using measured data from manufacturing sites collected between 1997 and 2011. The 90th percentile was used for the risk characterisation and for the purposes of the statistical analysis, all values below the limits of quantification (LOQ) were assigned a value 50% of the LOQ. The Registrants' values are consistent with those reported for manufacture in the 2003 SIAR.

Dermal exposure

Dermal exposure was assessed using the ECETOC TRA model V3 using conservative assumptions about the duration of tasks and assuming that the use of LEV has no impact on dermal exposures. Based on the process description, the eMSCA expects that tasks where workers may potentially come into direct contact with *p*-cresol will have a short duration and will not be performed for the whole shift. The eMSCA therefore expects that the dermal exposure values that have been calculated will most likely be overestimates.

The eMSCA considers that the inhalation and dermal exposure estimates provided for manufacturing are suitable to be used for the risk characterisation.

Use as an intermediate and use as a monomer in polymer production

The eMSCA does not have detailed descriptions of the OCs and RMMs that are in place at sites where *p*-cresol is used as an intermediate or as a monomer. However, based on the PROC codes that have been chosen for these scenarios, it expects that the process will be performed under similar conditions to those described for manufacture. This is consistent with the statement in CSRs that the process conditions are designed to minimise emissions of volatile organic compounds (VOCs).

The PROCs selected for these scenarios include PROCs 1, 3, 8b and 9. Exposure values were obtained using the ECETOC TRA tool V2 or 3 or measured data. The RMMs identified include the use of LEV (effectiveness based on tool defaults) protective clothing, closely fitting goggles/face shields and gloves with an assumed effectiveness of 90, 95% or 98%. Workers receive training in good practice and management systems and supervision is in place to ensure the correct procedures are followed.

Inhalation exposure

The eMSCA has been able to replicate inhalation exposure values with the exception of the value reported by some Registrants for PROC 1. These Registrants have assumed that LEV is in operation for this PROC code which is contrary to the approach taken in the TRA tool and this may explain the deviation from the eMSCA's value. In some cases,

where the ECETOC TRA tool V2 was used to assess inhalation exposure for tasks covered by PROCs 3 and 9, it has been necessary to limit the duration of the activity to achieve an RCR <1 without including requirements for RPE. Where this has been done, Registrants have included advice to employ containment or better ventilation if tasks are performed for longer durations. The eMSCA notes that it has been possible to achieve RCRs <1 if the duration modifier is not used for PROC 3, and that measured data from IFA (2012) suggests that the ECETOC TRA tool may be overestimating exposure in this case. Although the IFA (2012) dataset includes a high proportion of static samples, the processes covered in this scenario are carried out in predominantly closed conditions. Typically workers at such sites are unlikely to spend long periods on tasks involving direct exposure. In contrast, the sampling devices used to obtain static samples will be situated close to potential sources of emission for the duration of sample collection and therefore may overestimate personal exposure. Taking this into consideration, it seems reasonable to regard an exposure value derived from IFA (2012) as representative for full-shift exposures under the OCs and RMMs identified for use as an intermediate and use as a monomer in polymer production. Assessments based on higher values are likely to be very conservative.

The eMSCA also considers that the OCs and RMMs that are described for this scenario are sufficiently similar to those described for manufacturing to allow the 90th percentile of the short-term measurements reported by [redacted] to be applied to the use *p*-cresol as an intermediate and as a monomer in polymer production.

Dermal exposure

The same Registrants that reported a low value for PROC 1, also reported very low values for dermal exposure for PROCs 1 and 3 and it is not clear to the eMSCA what factors have been applied to the values reported by the ECETOC TRA tool V2 to achieve such low numbers. However, this may in part be explained if the use of LEV was also used as an exposure modifier for dermal exposure potential. Some Registrants assumed a glove effectiveness of 98% for transferring tasks covered by PROC 8b. All Registrants assumed task durations of up to 8 hours. Given that the use of *p*-cresol as an intermediate and as a monomer takes place under predominantly closed conditions, it seems likely that tasks requiring direct dermal contact will only occur for short durations during the day. For this reason, and taking all of the exposure values calculated for this scenario into consideration, the eMSCA is satisfied that suitable exposure values are available for dermal exposure for this scenario.

Formulation

The Registrants supply *p*-cresol to companies who prepare formulations of varnishes used for coating circuit boards and wire enamelling etc. The CSR also makes reference to the manufacture of construction chemcials in a multi-stage batch process.

The Registrants have characterised formulators as medium/large companies that handle *p*-cresol under predominantly closed conditions and have selected PROCs 1, 3, 5, 8b and 9 to cover the process. Communications between the Registrants and formulators during the evaluation year indicated that PROC 5 is not relevant and the Registrants intend to delete this PROC code from the scenario. The RMMs identified include the use of LEV (effectiveness based on tool defaults) protective clothing, closely fitting goggles/face shields and gloves with an assumed effectiveness of 90, 95% or 98%. Workers receive training in good practice and management systems and supervision is in place to ensure the correct procedures are followed.

Inhalation exposure

With the exception of PROC 1 which was assessed using the ECETOC TRA tool V3, the 8-hr TWA values used to characterise exposure during formulation are derived from IFA (2012) and the short-term values from [redacted]. Since the PROC codes selected for formulation are the same as those identified for the use of *p*-cresol as a

intermediate or as a monomer in polymer production, for the reasons already outlined, the eMSCA consideres that these measured data can be applied to the use of *p*-cresol in formuation.

Dermal exposure

Dermal exposure was assessed using the ECETOC TRA model V3 using conservative assumptions about the duration of tasks and assuming that the use of LEV has no impact on dermal exposures. Based on the process description, the eMSCA expects that tasks where workers may potentially come into direct contact with *p*-cresol will have a short duration and will not be performed for the whole shift. The eMSCA therefore expects that the dermal exposure values that have been calculated will most likely be overestimates.

Use in processing of solid and liquid polymers

This scenario covers the treatment/processing of solid and liquid polymers based on phenol/cresol derivatives and formaldehyde. This includes solid resole resins and liquid novolacs and epoxy-cresol novolac resins.

Resoles are base catalysed phenol-formaldehyde resins with a formaldehyde:phenol ratio greater than 1. Phenols (phenol, xylenol, cresols or alkylphenols), formaldehyde, water and catalyst are mixed and heated at around 70°C to form a thick reddish-brown tacky material. This is then heated to around 120°C which eliminates water and produces a resin with a 3-dimensional crosslinked structure. These resins may then be further processed by pressing, moulding or machining. Exposures during the mixing process have been assessed with the ECETOC TRA tool V2 or V3 using PROC 5 and during the further processing stages using PROCs 6 and 14 or with measured data. The Registrants have assumed that the maximum concentration of *p*-cresol in solid resins at the processing stage is 5% (w/w), but additional communication with downstream users suggests that in reality it is more likely to be <1% (w/w). The assumption of 5% (w/w) introduces conservatism into the exposure calculation.

Novolacs are made with an excess of phenolic compounds to formaldehyde and require the addition of hardening agents such as an organic amine to the liquid polymer to promote cross linking. During the evaluation, the Registrants obtained confirmation from downstream users that phenolics make up 1-10% (w/w) of the liquid resin systems. Since the phenolic component is a mixture, it has been assumed that *p*-cresol will be at most 50% (w/w) of the phenolic component and hence the assumption that *p*-cresol will be at a maximum concentration of 5% (w/w) of the resin system during processing is accurate.

Novolacs are commonly used for photolithography in the manufacture of circuit boards. Wafers are coated with novolac based photoresist systems either by brushing, dipping or spraying processes such as spin coating. Although PROCs 7, 10 and 13 have been used to cover these processes, in practice, circuit boards are manufactured in clean-room conditions to achieve a high quality product. The eMSCA expects that the measures that will be taken to minimise contamination will also limit the release of coating agents during application. PROC 5 has been used to cover mixing stages. The exposure values used to characterise the processing of liquid polymers derive from the ECETOC TRA tool V2 or 3, Stoffenmanager V3.5 (75th percentile vales) or measured data.

PROCs 8b and 9 have been used to cover transfers during the processing of solid and liquid polymers made using *p*-cresol. The exposure values used for these PROCs derive from Stoffenmanager V3.5 (75th percentile values, assuming *p*-cresol is present as a liquid) or measured data.

The RMMs identified include the use of LEV (effectiveness based on tool defaults) protective clothing, closely fitting goggles/face shields and gloves with an assumed effectiveness of 90, 95% or 98%. Workers receive training in good practice and

management systems and supervision is in place to ensure the correct procedures are followed. It was assumed that all contributing activities are performed for the full-shift.

Inhalation exposure

The eMSCA has been able to replicate the values used by the Registrants to assess inhalation exposure during processing of solid polymers. The eMSCA has also been able to replicate the values used by the Registrants to assess inhalation exposure during processing of liquid polymers, with the exception of values derived using Stoffenmanager V3.5. In this case, the eMSCA attempted to replicate the assessments using Stoffenmanager V6, the currently available version of this web based tool. The 75th percentile values obtained by the eMSCA were between 2 and 10 times higher than the values reported by Registrants using Stoffenmanager V3.5. This may be due to the way the concentration of *p*-cresol in formulations was taken into account. The measured data from IFA (2012) that has been provided as an alternative to modelled data suggests exposures may be higher than is suggested by Stoffenmanager V3.5 but will be lower than the values obtained by the eMSCA. Since the full shift inhalation exposure value derived from IFA (2012) is based on the LOQ for the analytical technique rather than actual measurements, it is not possible for the eMSCA to obtain any further insights from this measured data.

Short-term exposure values are based on the 90th percentile of the short-term measurements reported by [redacted] for the manufacture of *p*-cresol. These downstream processes have been assessed using different PROC codes to those selected for manufacture. It is not clear how closely the opportunites for short-term peak exposure for these processes match the short-term peak exposures covered by the measured data. Thus there is uncertainty about the respresentativeness of the measured short-term data for this scenario. However, the eMSCA also notes the low concentration of *p*-cresol in the resins that are being processed in comparison to the situations covered by [redacted] which provides some reassurance that the measured short-term data may tend to overestimate the exposures that are likely for this situation. This is supported by the very high percentage (98.7%) of measured data, including short term measurements, that were below the LOQ in the IFA dataset.

Based on the information currently available to the eMSCA and taking a collective view of all of the available information, the eMSCA considers that the exposure values being used to characterise inhalation exposures to *p*-cresol during processing of solid and liquid polymers are representative for the process.

Dermal exposure

The eMSCA has been able to replicate all of the values used by the Registrants to assess dermal exposure, with the exception of the value reported for PROC 7 by Registrants using the ECETOC TRA tool V3. Given that resoles are manufactured at high temperatures, it is expected that there will be no direct skin contact under normal operating conditions. It is also expected that skin contact with novolacs will be kept to a minimum to maintain a clean environment for the product. For these reasons, the eMSCA considers that the dermal exposure values quoted in the CSRs are likely to present a conservative picture.

Use as solvent in electric wire enamelling

Although the range of PROCs selected for this scenario suggests a potential for significant exposure, in reality it is a predominantly closed process and there are limited opportunities for workers to come into contact with the enamelling solutions[19].

[19] A description iof the process is available in a document produced for the European Commission to encourage substitution of volatile organinc solvents in the process, see (http://www.subsport.eu/images/stories/pdf_archive/legislation/14_guide_winding_wire.pdf).

Enamelling solutions are formulations containing a polymer resin based on polyesterimide or polyurethane ca. 25-50% (w/w) in a solvent mixture ca. 50-75% (w/w) which may contain phenols, cresols, xylenols, glycoderivatives, etc. Often these solvent mixtures are fractions obtained from tar distillation. Different solvent systems may be used depending on the thickness of wire being coated and the intended end-use. Cresols tend to be used for high molecular weight polymers where high temperature resistant coatings are required.

Enamelling solutions are delivered in $1m^3$ plastic intermediate bulk containers (IBCs) which are connected to a closed pipe system to transfer the enamel formulation to the enamelling machine. These are closed except for small 3-5 mm holes for the wire inlet and outlet ports. To minimise solvent emissions through these holes, enamelling machines operate under slight negative pressure. Enamelling machines are manufacutured to provide an inward airflow of 0.5 – 1 m/sec at these ports. The machine coats wires with a thin layer of the enamelling solution by immersion. Surplus enamel is removed by passing the coated wire through a die. For fine wires, the coating may be applied by pulling the wire through impregnated felts. Coated wires are then heated at temperatures up to 300°C to evaporate solvents from the coating and baked at temperatures of 400 - 700°C to cure the enamel. To achieve the desired thickness of enamel, this process may be repeated up to 30 times.

Solvent emissions from the wire enamelling process fall within the scope of the Solvent Emissions Directive (SED) (1999/13/EC). In order to maintain solvent emissions within the limits set by the SED, modern enamelling machines incorporate extraction ventilation and a catalytic or thermal oxidation process to minimise emissions. The heat that is generated from these oxidation processes feeds into the heating required for the solvent evaporation and baking stages.

The PROCs selected for this process include PROCs 1, 2, 3, 4, 8b, 9, 10 and 13. A subset of Registrants have also selected PROCs 5, 8a and 15. Exposure values for this process have been obtained using the ECETOC TRA tool V2 or 3 or measured data. The RMMs identified include the use of LEV (effectiveness based on tool defaults) protective clothing, closely fitting goggles/face shields and gloves with an assumed effectiveness of 90, 95% or 98%. Workers receive training in good practice and management systems and supervision is in place to ensure the correct procedures are followed.

Inhalation exposure

The eMSCA has been able to replicate the values used by the Registrants to assess inhalation exposure, with the exception of the value used for PROC 9 in some CSRs. This may be due to the way the Registrants have taken account of an effectiveness value for LEV of 98% which was assigned on the basis of information provided by downstream users. The tool default for this PROC code is 90%.

Note to Registrants: The eMSCA considers that it is rare that LEV systems will provide better than 95% effectiveness in operation unless they have been integrated into the equipment, properly maintained and tested regularly to ensure the high level of performance is maintained. The tool default has been set at 90% to reflect the reality that standards of installation, testing and maintenance can vary. Registrants that wish to continue to assign an effectiveness value of 98% to PROC 9 should provide additional supporting evidence to justify this choice.

Another description of the process is available from a UK government publication (http://webarchive.nationalarchives.gov.uk/20130123162800/http:/archive.defra.gov.uk/environment/quality/pollution/ppc/localauth/pubs/guidance/notes/sgnotes/documents/sg6-11.pdf).

In some cases, where the ECETOC TRA tool V2 was used to assess inhalation exposure for tasks covered by PROCs 3, 4, 5 and 8a, it has been necessary to limit the duration of the activity to achieve an RCR <1 without including requirements for additional RMMs. The measured data from IFA (2012) that has been provided as an alternative to modelled data, and which the Registrants confirm includes data collected from wire enamelling companies, suggests that the TRA tool is likely to overestimate inhalation exposure and that exposure to *p*-cresol can be managed adequately for a full shift using the RMMs described in CSRs.

In light of knowledge about the level of containment that is in use for wire enamelling, some Registrants opted to consider activities covered by PROCs 10 and 13 as closed processes and assessed exposures using the values for PROC 1. The eMSCA notes that this PROC is relevant for systems that are rigorously contained, including fixed pipe systems for transfers. Based on the process descriptions seen by the eMSCA, it is not clear that such a high level of containment can be assumed. The measured data suggests that exposures may be higher. However, since the full-shift inhalation exposure value derived from IFA (2012) is based on the LOQ for the analytical technique rather than actual measurements, it is not possible for the eMSCA to obtain any further insights. Further communication between the Registrants and downstream users during the evaluation year led to the identification of PROC 2 as providing a more realistic exposure estimate for this process. The eMSCA agreed with the Registrants that the process should still be described using PROCs 10 and 13, but that the exposure value for PROC 2 could be assigned since this provides a more realistic exposure estimate.

Short-term exposure values are based on the 90th percentile of the short-term measurements reported by Allmendinger (2012) for the manufacture of *p*-cresol. It is not clear how closely the opportunites for short-term peak exposure during wire enamelling match the short-term peak exposures covered by the measured data. However, the process description suggests that transfers may be the main potential source of exposure and transfers at dedicated facilities are covered by Allmendinger (2012).

Based the descriptions of the process that are available to the eMSCA and taking a collective view of all of the currently available information, the eMSCA accepts that the exposure values being use to characterise inhalation exposures to *p*-cresol during wire enamelling are representative for the process.

Dermal exposure

The eMSCA has not been able to replicate all of the values reported by Registrants using the ECETOC TRA tool V2 to assess dermal exposure but has been able to replicate the values derived using V3. Based on the process description, the eMSCA expects that tasks where workers may potentially come into direct contact with *p*-cresol will mainly be associated with transferring since the application and curing stages are automated. The process description suggests that tasks where there is the potential for direct skin contact will have a short duration, much shorter than has been assumed by Registrants using the ECETOC TRA tool V3. The eMSCA therefore expects that the dermal exposure values that have been calculated will tend to overestimate dermal exposure.

Laboratory use

This has been assessed using ECETOC TRA V2 or V3 as a contributing scenario within the wire enamelling activity or as a separate scenario. The RMMs identified for this use include use of a fume cupboard supported by good general ventilation in the laboratory and the use of gloves with an assumed effectiveness of 90%. The eMSCA has been able to replicate the values used by the Registrants in some cases but not all. This may be because in some cases an effectiveness of 98% has been assumed for the fume cupboard instead of the tool default of 90%. Since the eMSCA has been able to replicate the least conservative values, it is satisfied with the exposure assessment for this scenario.

Note to Registrants: In relation to the assumed effectiveness of 98% for a laboratory fume hood, given that the effectiveness of laboratory fume hoods is very dependent on the degree to which the hood is left open by an individual user, the eMSCA does not consider that it is appropriate to assume a higher effectiveness than the tool default.

7.12.1.2 Consumer

Consumer exposure from the uses covered in these registrations only occurs during the service life of plastic articles where *p*-cresol is one of the starting monomers used to manufacture the plastic. The CSRs state that such plastics may be used to produce a variety of different articles including electrical and electronic products and food packaging[20]. The exposure assessment assesses consumer exposure at a regional rather than individual level. It is assumed that the service life of a typical article is 10 years and that over the 10 year period, all residual monomer will be released from the article. It is also assumed that all of the lost *p*-cresol is available for inhalation. This approach does not take account of losses of residual monomer during the manufacture of the article and the eMSCA accepts the Registrants' view that the calculation is likely to represent a worst case situation.

Dermal exposure is assumed to be negligible on the grounds that contact times with articles such as batteries will be less than once per day for a few seconds and with other plastic articles will occur around 5 times per day with durations of a few minutes per contact. Oral exposure is also assumed to be negligible on the basis that batteries are not intended to be mouthed and that mouthing of other plastic articles will take place less than once per day for a few seconds. Although the eMSCA does not have comprehensive information about the article types that may be made with plastics manfuactured using *p*-cresol as a monomer to know whether the assumptions about dermal and oral contact times are appropriate, the eMSCA considers that the oral and dermal exposures arising from this scenario are unlikely to make a meaningful contribution to the levels of dermal and oral exposure expected from dietary and other environmental sources of *p*-cresol.

The eMSCA notes that a specific scenario addressing potential professional exposure has not been developed. Professionals may be exposed to the same article types that have been assessed for consumers, but the intensity of exposure may be greater. In particular, professionals engaged in maintenance and repair (also end of life recycling of old electrical articles) may handle articles made using *p*-cresol based polymers to a greater extent than has been assumed for consumers. Given that the consumer exposure assessment is based on worst case assumptions about the quantities of *p*-cresol released from articles, the eMSCA considers that the consumer exposure assessment is likely to encompass potential professional exposure and does not consider it is necessary for the Registrants to carry out further work in respect of this potentially exposed group.

[20] p-Cresol is listed in Annex I of Commission Directive 90/128/EEC relating to plastic materials and articles intended to come into contact with foodstuffs as an authorised monomer (PM/REF No 14770) with no restrictions. REACH article 14(5)(a) states that risks to human health arising from use in food contact materials within the scope of Regulation (EC) No 1935/2004 do not need to be addressed in the CSR.

7.12.2. Environment

1. **Not assessed.**

7.12.3. Combined exposure assessment

The registrants have not carried out an exposure or risk assessment for combined exposures to humans. Given that dietary and other sources not covered in REACH registrations are expected to exceed daily exposures from the use of articles and exposures via the environment arising from specifically uses covered in REACH registrations, the eMSCA does not consider it is necessary for the Registrants to carry out further work on this topic.

7.13. Risk characterisation

Human Health

The lead health concern for the risk characterisation is corrosivity/irritation. The Registrants have taken different approaches to deal with this concern. Some have derived DNELs for systemic endpoints and taken a qualitative approach to address corrosivity/irritation. Others have used information from routine workplace health surveillance to identify a provisional NOAEC of 0.9 mg/m^3 for respiratory tract irritation and have taken a quantitiative approach.

The eMSCA has not calculated its own DNELs for inhalation or dermal exposure because it considers that it is not possible to identify sufficiently reliable LOAEC/NOAEC values and prefers to take a qualitative approach to the risk characterisation. *p*-cresol is considered to have moderate hazard due to its acute toxicity (attracting classification with H301 and H311) and its corrosivity (attracting classification with H314). The IR & CSA Guidance, Part E, table E.1 indicates that for such substances, measures should be in place to limit release using containment or exhaust ventilation as appropriate. Based on the information in CSRs this appears to be the case for *p*-cresol. It is also important to minimise the numbers of staff potentially exposed, ensure that they are trained in good working practices and that suitable management and supervision is in place to ensure the RMMs are being used correctly and good practices followed. To minimise skin contact, suitable gloves and protective clothing should be provided and eye/face protection should be worn where there is the potential for splashing to occur. These requirements are reflected in the CSRs.

The exposure levels that have been calculated for consumers are substantially below levels where irritation or systemic effects are likely to occur and the eMSCA does not identify concerns for consumers exposed via the service life of articles. Although professionals could potentially receive higher exposures from handling articles which may contain *p*-cresol residues, the eMSCA does not expect there is any potential for irritation or systemic effects will arise as a result of these potential exposures and does not identify concerns for professionals. Overall, the eMSCA does not identify concerns for the registered uses of *p*-cresol and is satisfied that the OCs and RMMs that have been identified for all users are appropriate.

7.14. Additional information

UK CA literature search for human health

To ensure that the dossier included all relevant publications, the eMSCA performed a literature review on *p*-cresol (human health effects). The strategy for the review was to search for *p*-cresol and its synonyms in conjunction with defined key words that are

specific to the areas identified as a concern in the CoRAP. Two databases were employed which cover many areas of science (Pubmed and Toxnet).

The following search terms were adopted for Pubmed:

((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (mutagenicity OR genotoxicity OR mutagen* OR genotox*)

((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (Canc* OR carc* OR tumo)

((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (repro* OR reprotox* OR fert* OR devel*)

((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (endo* OR endocrine OR disruptor)

The following search terms were adopted for Toxnet:

1. ((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (mutagenicity OR genotoxicity OR mutagen* OR genotox*)

2. ((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (carcino* OR tumo)

3. ((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (reprotox* OR fert* OR devel*) plus ((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (repro*)

4. ((4-methylphenol OR *p*-cresol OR para-cresol OR 4-cresol OR 4-hydroxytoluene OR 106-44-5 OR 203-398-6)) AND (endocr* OR disruptor)

The total number of returns is listed below for each database. An initial screen of the titles only was performed; any remaining records were downloaded and assessed for relevance based on their abstracts. A full assessment of the article was completed if relevant following the first two screens.

Results from Pubmed:

Data requirement(s) captured in the search	Pubmed
Total number of summary records retrieved after all* searches of peer-reviewed literature (excluding duplicates)	561
Number of summary records excluded from the search results after rapid assessment for relevance	554
Total number of abstracts assessed	7
Number of studies excluded from further consideration after detailed assessment for relevance	5
Number of studies not excluded for relevance after detailed assessment (i.e. relevant studies and studies	2

of unclear relevance)	

Results from Toxnet

Data requirement(s) captured in the search	Toxnet
Total number of summary records retrieved after all* searches of peer-reviewed literature (excluding duplicates)	2346
Number of summary records excluded from the search results after rapid assessment for relevance	2335
Total number of abstracts assessed	11
Number of studies excluded from further consideration after detailed assessment for relevance	8
Number of studies not excluded for relevance after detailed assessment (i.e. relevant studies and studies of unclear relevance)	3

The 18 abstracts from the pubmed and Toxnet searches were reduced to 5 after reading the abstracts as 13 publications were either reviews of the available studies in the registrant's dossier, referenced directly within the submission, were deemed not related to the main areas of assessment or were duplicates across the two databases.

The remaining five articles were as follows:

Terasaka S et al, "Expression profiling of estrogen-responsive genes in breast cancer cells treated with alkylphenols, chlorinated phenols, parabens or bis- and benzoylphenols for evaluation of estrogenic activity" Toxicology Letters 2006, 163: 136-141. Included in section 7.10.2.

Heindel J et al, "*m/ p*-cresol" Environmental Health Perspectives 1997, 105: 295-296.

Litton Bionetics Inc 1980, "Mutagenicity evaluation of sample containing 33 1/3 % each ortho-, meta-, and para-cresol in sister chromatid exchange assay with Chinese hamster ovary (CHO) cells FINAL report"

Litton Bionetics Inc 1980, "Mutagenicity evaluation of sample containing 33 1/3 % each ortho-, meta-, and para-cresol in mouse lymphoma forward mutation assay FINAL report"

Litton Bionetics Inc 1980, "Mutagenicity evaluation of sample containing 33 1/3 % each ortho-, meta-, and para-cresol in primary rat hepatocyte unscheduled DNA synthesis assay draft report"

The studies by Heindel and Terasaka have been included in the relevant section in the report but the studies by Litton laboratories could not be found by the eMSCA as these are study reports not freely available and the conducting facility has been disbanded. Additional publications identified during the evaluation have been noted in the report.

7.15. Abbreviations

%	Percentage
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
ATH	Atypical tubule hyperplasia
CLP	Classification, labelling and packaging (of substances and mixtures)
cm	Centimetre
CoRAP	Community Rolling Action Plan
CPN	Chronic progressive nephropathy
CSR	Chemical Safety Report
d	Day
DMEL	Derived Minimal Effect Level
DNEL	Derived No Effect Level
DSD	Dangerous Substances Directive
ECETOC TRA	European Centre for Ecotoxicology and Toxicology of Chemicals Targeted Risk Assessment
ECHA	European Chemicals Agency
eMSCA	evaluating Member State Competent Authority
EPA	Environmental Protection Agency
ES	Exposure Scenario
EU	European Union
g	Gramme
GC	Gas chromatography
GC/FID	Gas chromatography – Flame Ionisation Detection
GC/MS	Gas chromatography – mass spectrometry
GLP	Good laboratory practice
hPa	Hectopascal
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database
IUPAC	International Union of Pure and Applied Chemistry
kg	Kilogram
kJ	Kilojoule
km	Kilometre
kPa	Kilopascal
K_{ow}	Octanol-water partition coefficient
L	Litre
LEV	Local Exhaust Ventilation
Log	Logarithmic value

LOD	Limit of detection
LOQ	Limit of quantitation
M	Molar
m	Metre(s)
µg	Microgram
mg	Milligram
min	Minute
mL	Millilitre
mol	Mole
MS	Mass spectrometry
MSCA	Member State Competent Authority
m/z	Mass to charge ratio
nm	Nanometre
NOAEL	No observed adverse effect level
NOEC	No-observed effect concentration
NOEL	No observed effect level
OC	Operational condition
OECD	Organisation for Economic Co-operation and Development
p	Statistical probability
Pa	Pascal
PC	Product category
pg	Picogram
pKa	Acid dissociation constant
ppb	Parts per billion
PPE	Personal Protective Equipment
ppm	Parts per million
PROC	Process Category
QSAR	Quantitative structure-activity relationship
r^2	Correlation coefficient
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals (EU Regulation No. 1907/2006)
RCR	Risk characterisation ratio
RMM	Risk Management Measures
RPE	Respiratory protective equipment
t	Tonne
TEDX	Endocrine Disruption Exchange
TG	Test Guideline
UK	United Kingdom
UV	Ultraviolet

WHO	World Health Organisation
wt.	Weight

7.16. References

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