AR201-13885

Barbara Christianson <BChristianson@lawbc.com> on 07/29/2002 03:26:36 PM

To: NCIC OPPT/DC/USEPA/US@EPA, Rtk Chem/DC/USEPA/US@EPA
cc: Richard Hefter/DC/USEPA/US@EPA

Subject: Merisol -- HPV Challenge Program (EPA Registration No.)

Appended is Merisol's submission on its proposed category approach and test plan for the Ethylphenols Category under the HPV Challenge Program. Please let us know if you have any questions.

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July 29, 2002

Via E-Mail and Regular Mail

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22116

Re: HPV Challenge Program Submission by Merisol --
EPA Registration No _____

Dear Administrator Whitman:

As part of Merisol USA LLC's (Merisol) commitment under EPA's High Production Volume (HPV) Challenge Program, Merisol is pleased to submit its proposed category approach and test plan for the Ethylphenols Category. The Ethylphenols Category consists of the following three chemicals:

o-ethylphenol (CAS No. 90-00-6)
p-ethylphenol (CAS No. 123-07-9)
m-ethylphenol (CAS No. 620-17-7)

Merisol understands that the category justification and test plan will be posted on the Internet and subject to a 120-day comment period. It is Merisol's further understanding that all comments by EPA or received by EPA will be forwarded to Merisol for consideration. This submission is also being sent electronically to the following e-mail addresses:

oppt.ncic@epa.gov
chem.rtk@epa.gov

Thank you for your assistance in this matter. If EPA requires any additional information, please contact Lisa Campbell at (202) 557-3802 or lcampbell@lawbc.com.

Sincerely,

Kenneth P. Morgan
Manager Technical Support Services
Merisol USA LLC

Attachment
cc: Mr. Richard H. Hefter, Jr. (w/attachment) (via e-mail)

AR201-13885A

U.S. EPA HIGH PRODUCTION VOLUME CHEMICAL VOLUNTARY TESTING PROGRAM

CATEGORY JUSTIFICATION AND TEST PLAN

ETHYLPHENOL ISOMERS

Submitted by:
MERISOL USA LLC
Houston, Texas

July 29, 2002

INTRODUCTION

Ethylphenols

Ethylphenols are liquids or crystals recovered from petroleum streams, coal coking operations and coal gasification. There are three isomeric forms of ethylphenol: o-, m-, and p-ethylphenol. The boiling points for o-, m-, and p-ethylphenol are 204.6ºC, 218.0ºC and 218.4ºC, respectively.

Merisol's Process

Merisol's phenolic products are highly versatile materials that are used as intermediates in the manufacture of a wide variety of industrial products such as resins, flame retardants, antioxidants, and insulating varnishes. Merisol production of phenolics is essentially a recovery, purification, and fractionation operation. Merisol feedstocks are generally secondary streams from refineries, coal coking operations and coal gasification. From these feedstocks a multi-component phenolic mixture called "crude cresylic acid" is produced, which is composed of phenol, cresols, xylenols, ethylphenols, and, to a lesser extent, other higher boiling alkyl phenols. This mixture is processed to remove impurities, and then separated into various fractions by distillation. Distillation produces phenol, o-cresol, m- and p-cresol mixture, and fractions containing varying compositions of xylenols, ethylphenols, and higher boiling alkyl phenols. Merisol also has a proprietary process that produces p-cresol and m-cresol from the m-cresol and p-cresol mixture produced by distillation. Because of similarities in boiling points of components in the starting phenolic mixture, isolation of all pure m- and p-ethylphenol isomers by distillation is not possible.[1] Isolation of the o-ethylphenol isomer by distillation is possible, but has not proved to be commercially viable.

Exposure Pattern for the Ethylphenols

Merisol sells pure phenol, o-cresol, m-cresol and p-cresol. These are also sold in blends, as are the mixtures of ethylphenols and xylenols. Merisol produces and sells ethylphenols contained in mixtures and does not sell or distribute any isomer of these as isolated materials in HPV threshold quantities. Therefore, public (and employee) exposure, as well as potential environmental exposures to Merisol's products, are only to blends and mixtures containing ethylphenols. Because these Merisol products are generally moved into commerce as starting materials for further chemical processing, there is little consumer exposure to ethylphenols. Merisol is by far the major, if not sole, U.S. producer of ethylphenols.[2]

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[1] For the same reason, as discussed in Merisol's concurrently submitted proposal for mixed xylenols, isolation of all pure xylenol isomers by distillation is not possible.

[2] Merisol understands that in the past, another company may have imported amounts of up to 600,000 pounds per year of pure p-ethylphenol that were used as an intermediate in producing another substance; however, this activity may no longer take place. Merisol also understands that another company may be using amounts up to 20,000 pounds per year of pure m-ethylphenol. Merisol has no information concerning, or basis to believe there is, any current production or importation of pure o-ethylphenol.

Merisol is a custom blender of phenolics. The number of different phenolic mixtures Merisol typically produces in a year is approximately 50, but can go as high as 100. These mixtures contain varying compositions of phenol, cresols, xylenols, ethylphenols, and higher boiling alkyl phenols. Ethylphenols, as well as xylenols, phenol, and cresols, are not components of every Merisol product mixture.

A breakdown of numbers of ethylphenol isomers contained in product mixtures is given in Text Table 1. Table 1 illustrates that Merisol products containing virtually all of the ethylphenol produced by Merisol are sold in products containing at least two of the three ethylphenol isomers.

Table 1: Distribution of Individual Ethylphenol Isomers In Merisol Products

	Number of Different Ethylphenol Isomers Present as Components in Merisol Products		
	1 ethylphenol isomer in product	2 ethylphenol isomers in product	3 ethylphenol isomers in product
% of total ethylphenol placed into commerce by Merisol	0.6	42.3	57.1

DESCRIPTION OF THE CATEGORY

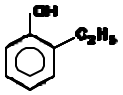
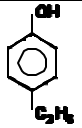
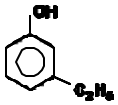
Ethylphenols

Ethylphenols are liquids or crystals recovered from petroleum streams, coal coking operations, and coal gasification. There are three isomeric forms of ethylphenol: o-, m-, and p-ethylphenol. Each of these isomers appear in the EPA HPV list of chemicals to be evaluated. Identification of the isomers appears in Text Table 2, below. For purposes of the Ethylphenols Category, Merisol is defining ethylphenols as a mixture containing equal portions of:

o-ethylphenol (CAS # 90006)
p-ethylphenol (CAS# 123079)
m-ethylphenol (CAS# 620177).

This mixture is intended to represent the Category "Ethylphenols" for HPV data development, as well as each separate ethylphenol isomer. Each isomer is represented in the Category. Data developed on this Category are intended to represent all mixtures of ethylphenol, as well as the individual ethylphenol isomers.

Table 2 Ethylphenols – Chemical Name, CAS Number, and Structure

Chemical	o-Ethylphenol	p-Ethylphenol	m-Ethylphenol
CAS Registry Number	90006	123079	620177
Molecular Structure			

CATEGORY JUSTIFICATION

ETHYLPHENOLS

As structural isomers, the members of the Ethylphenols Category share the same molecular weight, or in the case of the mixture, average molecular weight. The substituent groups on the phenolic ring are always ethyl groups, so branching differences among the side groups is not a possibility in this Category. Examination of the physical-chemical properties for each isomer (Text Table 3) shows that the physical-chemical properties of the isomers are quite similar, due to the structural similarities. Of particular importance to environmental effects and potential human health effects are the values for octanol/water partition coefficient and water solubility. The values for octanol/water partition coefficient are 2.40 to 2.58 for each of the ethylphenol isomers. Ethylphenols appear to be relatively water soluble: the water solubility value at 25°C for p-ethylphenol is 4900 mg/L and for o-ethylphenol, 5340 mg/L. These values suggest that ethylphenol isomers and mixtures of isomers will distribute similarly in the environment and have similar residence times in environmental compartments. Bioaccumulation attributes will be similar among the isomers and the mixture also. Vapor pressures of the isomers at 25ºC range from 0.050 to 0.153 mmHg for the ethylphenols, also supporting a similar pattern of airborne distribution. Individually and as a group the ethylphenols are expected to exhibit low-to-moderate mobility in soil based on the $K_{o/w}$ values. Hydrolysis values have not been reported for ethylphenols, presumably due to the absence of a hydrolyzable functional group. Within the family of ethylphenol isomers, the physicochemical properties are expected to manifest similar effects on the environment and potentially on human health.

The biological response patterns of ethylphenols, like the physicochemical properties, derive from the structural similarities of the isomers. There are data from independent sources to support this position by way of example or illustration. For instance, in work completed by the National Toxicology Program (NTP) with a group of structurally-related isomers, in this case methyl phenols, or cresols, toxicology studies showed that there was no one predominantly toxic isomer and that target organs for toxicity and toxic effect dose levels were relatively consistent across the isomers. This is expected to be the case for ethylphenols.

Table 3: Ethylphenols Physical Properties

Chemical	o-Ethylphenol	p-Ethylphenol	m-Ethylphenol
CAS Registry Number	90006	123079	620177
Boiling Point	204.6ºC	218.0ºC	218.4ºC
Melting Point	18ºC	-4ºC	46ºC
Density	1.014 @ 25ºC	1.028 @ 20ºC	1.011 @ 20ºC
Oil/Water Partition Coefficient	2.47	2.58	2.40
Water Solubilty	5340 mg/L @ 25ºC	4900 mg/L @ 25ºC	Slightly soluble
Vapor Pressure	0.153 mmHg@ 25ºC	0.089 mmHg@ 25ºC	0.050 mmHg@ 25ºC
$K_{o/w}$	530	480	600
Photodegradation in Air	$T_{1/2}$ = 9 hrs.	$T_{1/2}$ = 5 hrs.	$T_{1/2}$ = 9 hrs.

Toxicological Justification for the Ethylphenols Category

Ethylphenols are closely structurally related to methyl phenols, which are also known as cresols. The toxicological justification for the Ethylphenols Category is that existing studies of methyl phenols have demonstrated that the methyl phenol isomers are remarkably equivalent in toxicity and that binary and tertiary mixtures of cresol isomers do not produce toxic interactions among the isomers, *i.e.*, that mixtures of cresol isomers do not exhibit more than additive toxicity.[3] Attachment 1 to this document presents in tabular form summaries of developmental

[3] In 28-day feeding studies conducted on cresol isomers by the NTP, mice and rats were treated with equivalent dose levels of each isomer and in 90-day studies rats received equivalent doses of ortho-cresol or the meta/para-mix. The author of the study, Dennis Dietz, observed so little difference among the cresol isomers in toxicity (both concentration and dose effects) that he chose to summarize the results of the 28- and 90-day studies together. In summarizing the subchronic toxicity of cresol isomers, Dietz said:

> The cresol isomers exhibited a generally similar pattern of toxicities in rats and mice. Dietary concentrations of 3,000 ppm appeared to be minimal effect levels for increases in liver and kidney weights and 15,000 ppm for deficits in liver function. Histopathologic changes, including bone marrow hypocellularity, irritation to the gastrointestinal tract and nasal epithelia, and atrophy of female reproductive organs, occasionally occurred at 10,000 ppm, but were more common at the high dose of 30,000 ppm (Ref. NTP, 1992).

In these studies, which included an assessment of individual isomers and an isomer mix, no evidence of toxic interaction was reported by the author, Dietz. In the final report of those studies, Dietz concluded that "In summary, the various cresol isomers exhibited a generally similar spectrum of toxicities in these studies, with few exceptions as noted previously. There was little evidence to suggest a significant increase in toxicity with longer exposures in the 13-week study when compared to the effects seen with similar doses in the 28-day study."

and reproductive toxicity data, as well as genetic toxicity data on methyl phenol isomers. From inspection of the Attachment 1 tables, it can be seen that within a test animal species (rabbit or rat), methyl phenol (cresol) isomers exhibited similar or the same toxicity. Effective doses, expressed as NOAELs, remained constant or very close across isomers, never more than one dose level apart. Target organs for isomer toxicity and systemic toxic effects were nearly superimposable across isomers. This qualitative and quantitative comparability of toxicity across isomers exhibited in the cresols data set is consistent with cresol isomers results described by Dennis Deitz, cited in the footnote above. Genetic toxicity studies of the cresol isomers show few inconsistencies in test results across isomers. In the seven cases where there are data on a mixture of the isomers, as well as data on one or more isomers, there is no difference in results in those cases (two) where data are available on each isomer and the mixture. In another case, the positive assay result for the mixture can be attributed to a positive result for an isomer in the same test. In the remaining four examples, isomeric uniformity of genetic activity cannot be affirmed or refuted because of the incomplete data set.

The toxicological equivalence or near equivalence of methyl phenols (cresols) derives from the structural similarity shared by members of the group (isomeric forms of methyl phenol) and the similarity in chemical/physical properties which follows from the structural relationship. In an analogous manner, a complementary structure-activity relationship is anticipated with ethylphenols based on the structural similarity among this group of isomers. The demonstration of a structure-activity relationship among the methyl phenol isomers and the expectation of a parallel structure-activity relationship for the homolog ethylphenols is the toxicological justification of the Ethylphenols Category for HPV testing.

CATEGORY TEST PLAN

Details for the toxicological work on ethylphenols are unavailable. Thus, while the existing mammalian and ecological toxicology data, when viewed as a whole, strongly support toxicology data development on an ethylphenol mixture as a category for HPV testing, the data may not in every case be adequately reported to be relied upon for HPV evaluations. Accordingly, Merisol proposes that no existing studies will be used to supply data for SIDS endpoints in the Ethylphenols Category. Merisol is not relying on data developed on analogous compounds to satisfy Ethylphenols Category testing but instead will develop data for each SIDS Screening Endpoint using the ethylphenol isomer mixture identified above and shown again below:

Merisol is defining ethylphenols as a mixture containing equal portions of:

o-ethylphenol (CAS # 90006)
p-ethylphenol (CAS# 123079)
m-ethylphenol (CAS# 620177).

This mixture is intended to represent the Category “Ethylphenols” for HPV data development, as well as each separate ethylphenol isomer. Data developed on this Category are intended to satisfy all requirements under the HPV Challenge Program for all mixtures of ethylphenols, as well as the individual ethylphenol isomers.

The HPV testing proposed by Merisol for the Ethylphenols Category is shown in Text Table 5.

CONCLUSION

Ethylphenol mixtures sold or distributed in the U.S. by Merisol are of variable composition. Testing every possible variation would violate animal use goals without producing additional meaningful scientific information, and would thus also be unnecessarily burdensome. Because exposure of people and the environment is to mixtures of ethylphenols, data developed on a mixture of three ethylphenols will provide cogent and reliable information for assessment of the potential hazards its ethylphenol-containing products may present to humans and the environment. This approach to data development also will account for any interactions between ethylphenol isomers that may impact toxicity, although none are expected.

Merisol proposes a category approach for testing ethylphenols. The testing is to account for each of the ethylphenol listings on EPA's HPV list of chemicals to be tested.

Table 5: Ethylphenols Category HPV Test Plan

HPV DATA ENDPOINT	PROPOSED DATA DEVELOPMENT METHOD
1. CHEMISTRY	
Melting Point*	OECD Test Guideline 102
Boiling Point*	OECD Test Guideline 103
Vapor Pressure	OECD Test Guideline 104
Water Solubility	OECD Test Guideline 105
Partition Co-Efficient	OECD Test Guideline 107
2. ENVIRON-MENTAL FATE	
Photodegradation	Estimate/model
Hydrolysis (Stability in Water)	OECD Test Guideline 111
Biodegradation	OECD Test Guideline 301
Fugacity	Fugacity Level III Modeling
3. HEALTH EFFECTS	
Acute Toxicity	Acute Oral Toxicity: OECD Health Effects Test Guideline 401**
Repeat Dose Toxicity	Combined Repeat-Dose Toxicity Study with Reproductive/ Developmental Toxicity Screen: OECD Health Effects Test Guideline 422
Repro-Develop. Toxicity	
Genetic Toxicity	Bacterial Mutation Test: OECD Health Effects Test Guideline 471 Mammalian Erythrocyte Micronucleus Test: OECD Health Effects Test Guideline 474
4. ECOTOXICITY	
Fish	Acute Toxicity to Fish: OECD Test Guideline 203
Daphnia	Acute Toxicity to Aquatic Invertebrates: OECD Test Guideline 202
Algae	Acute Toxicity to Aquatic Plants (Algae) : OECD Test Guideline 201

** Since the test material is a mixture of isomers, melting point and boiling point will be reported as a range of values.
** Alternative testing proposed by OECD (November 21, 2001, OECD Joint Meeting of the Chemical Committee and Working Party on Chemicals, Pesticides and Biotechnology) may be employed. Alternative tests are OECD Test Guidelines 420, 423 or 425.

REFERENCES

NTP Report on the Toxicity Studies of Cresols in F344/N Rats and B6C3F1 Mice. Dennis Dietz, US Department of Health and Humans Services, February, 1992.

ATTACHMENT 1

Mammalian reproductive/developmental toxicity summaries and genetic toxicity summaries of methyl phenol isomers (o-, m-, and p-cresol)

CRESOLS ISOMER MAMMALIAN TOXICITY COMPARISON

STUDY NOAEL	o-CRESOL	m-CRESOL	p-CRESOL
Rabbit Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	5 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	5 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	5 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes; 15% and 35% mortality in mid- and high-dose vs. 0% in controls.
Rabbit Oral Gavage Developmental Toxicity: Developmental NOAEL & Effect/Target Organ	50 mg/kg/day No embryotoxicity or fetotoxicity. Skeletal variations observed in mid- and high-dose pups	100 mg/kg/day No embryotoxicity or fetotoxicity.	100 mg/kg/day No embryotoxicity or fetotoxicity.
Rat Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	175 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 16% mortality.	175 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 0% mortality.	175 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 12% mortality.
Rat Oral Gavage Developmental Toxicity: Developmental NOAEL & Effect/Target Organ	175 mg/kg/day No increase in malformations, visceral variations at the high-dose.	450 mg/kg/day No increase in malformations. No increase in variations.	175 mg/kg/day No increase in malformations, skeletal variations at the high-dose.
Two-Generation Reproductive Toxicity In Rats by Oral Gavage: Parental NOAEL & Effect/Target Organ	30 mg/kg/day Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 52%-28% mortality across sexes and generations. No lesions specifically noted in organs from F0 and F1 adult necropsy.	<30 mg/kg/day Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 40%-12% mortality across sexes and generations. Brain hemorrhage, atrophied seminal vesicle, lung congestion noted at necropsy of F0 but not F1 parents.	30 mg/kg/day Transient hypoactivity, audible respiration, ataxia, twitches, tremors, initially decreased food consumption and body weight gain, 40%-4% mortality across sexes and generations. Lung congestion noted at necropsy of F0 parents, atrophied seminal vesicle and lung congestion noted at necropsy of F1 parents.
Two-Generation Reproductive Toxicity In Rats by Oral Gavage: Offspring NOAEL & Effect/Target Organ	175 mg/kg/day No gross lesions in F1 or F2 pups.	175 mg/kg/day No gross lesions in F1 or F2 pups.	175 mg/kg/day No gross lesions in F1 or F2 pups.

SUMMARY OF CRESOLS MUTAGENICITY DATA

ASSAY	TEST SUBSTANCE			
GENE MUTATION	ORTHO	META	PARA	MIXED
SALMONELLA ACTIVATION	-	-	-	-
SALMONELLA NONACTIVATION	-	-	-	-
MOUSE LYMPHOMA ACTIVATION	-	nd	nd	+
MOUSE LYMPHOMA NONACTIVATION	-	nd	nd	nd
*MOUSE LYMPHOMA ACTIVATION	nd	-	-	nd
*MOUSE LYMPHOMA NONACTIVATION	nd	-	-	nd
*SLRL DROSOPHILA	-	nd	-	nd
DNA EFFECTS				
UDS	-	nd	+	+
*HEPATOCYTE UDS	nd	-	nd	nd
CHROMOSOME DAMAGE				
ROOT TIP	+	+	+	nd
SCE ACTIVATION	?	-	-	+
SCE NONACTIVATION	?	-	-	+
*CHO CYTOGENETICS ACTIVATION	+	-	+	nd
*CHO CYTOGENETICS NONACTIVATION	+	-	+	nd
*MOUSE (IN VIVO) CYTOGENETICS	nd	-	nd	nd
*MOUSE DOMINANT LETHAL	-	nd	-	nd
MOUSE MICRONUCLEUS				-
CELL TRANSFORMATION				
BALB/C 3T3 ACTIVATION	-	nd	nd	+
*BALB/C 3T3 ACTIVATION	-	-	nd	nd
*BALB/C 3T3 NONACTIVATION	nd	-	+	nd
C3H10T1/2 ACTIVATION	nd	nd	+	nd
C3H10T1/2 NONACTIVATION	nd	nd	nd	nd

* ACC PANEL ASSAYS

nd = No Test Data
+ = Positive for Genetic Toxicity
- = Negative for Genetic Toxicity
? = Equivocal Results for Genetic Toxicity

REFERENCES: ATTACHMENT 1

Developmental Toxicity and Reproductive Toxicity References:

R. W. Tyl, Unpublished Report Number 51-508: "Developmental Toxicity Evaluation of o-, m-, or p-cresol Administered by Gavage to New Zealand White Rabbits," Bushy Run Research Center, Export, Pa., June 27, 1988.

R. W. Tyl, Unpublished Report Number 51-509: "Developmental Toxicity Evaluation of o-, m-, or p-cresol Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., June 29, 1988.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-634: "Two Generation Reproduction Study of m-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., February 28, 1989.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-614: "Two Generation Reproduction Study of o-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., December 19, 1989.

T. L. Neeper-Bradley and R. W. Tyl, R. W. Tyl, Unpublished Report Number 51-512: "Two Generation Reproduction Study of p-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., March 28, 1989.

Genetic Toxicity References:

IUCLID Data Sheet: o-Cresol CAS Number 95-48-7, European Chemicals Bureau, February 11, 2000.

IUCLID Data Sheet: m-Cresol CAS Number 103-39-4, European Chemicals Bureau, June 19, 1997.

IUCLID Data Sheet: Mixed Cresols CAS Number 1319-77-3, European Chemicals Bureau, March 1, 2001.

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APPENDIX A
ROBUST SUMMARY FOR m-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

REPEATED DOSE TOXICITY

Type	:	Repeated dose
Species	:	Rat
Sex	:	Male
Strain	:	no data
Route of admin.	:	oral feed
Exposure period	:	28 d
Frequency of treatm.	:	Daily
Post exposure period	:	No
Doses	:	0, 20, 150, 500 mg/kg diet (approx. 0, 1.86, 13.95 or 45.8 mg/kg bw/d)
Control group	:	yes, concurrent no treatment
NOAEL	:	ca. 45.8 mg/kg bw
Method	:	other: 10 rats/group, TS was prepared as a 2.0% corn oil solution and blended with the diet; diets were prepared fresh weekly. Control rats received basal diets containing 2% corn oil, necropsy of all animals
Year	:	1969
GLP	:	no data
Test substance	:	other TS: M.P.:11-12 C; B.P.: 202.8 C
Result	:	No deaths occurred during the study and no untoward behavioural reactions were noted. At necropsy, no significant gross lesions were noted among the test animals, when compared to the control animals.

(1)

Type	:	Repeated dose
Species	:	Rat
Sex	:	male/female
Strain	:	other: F344/N
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	continuously in diet
Post exposure period	:	No
Doses	:	0, 300, 1000, 3000, 10000 or 30000 ppm (see remarks)
Control group	:	Yes
NOAEL	:	10000 ppm
Method	:	other: 5 rats/sex and dose, clinical observations twice daily, body weight initially, weekly and at termination, gross and microscopic examination, statistical analysis
Year	:	1991
GLP	:	Yes
Test substance	:	other TS: purity > 98%
Remark	:	mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	25	25
1000 ppm	85	82
3000 ppm	252	252

		10000 ppm 870 862 30000 ppm 2470 2310
Result	:	no mortallity; no clinical signs of toxicity were observed and no gross lesions were noted at necropsy >= 10000 ppm: increased relative liver weights for males and females, but no histomorphologic changes 30000 ppm: decreased mean final body weights and mean body weight gains for males and females; reduced food consumption in males and females during the first week of the study; relative kidney weight marginally increased in males and females but no histomorphologic changes; minimal to mild uterine atrophy in 4 of 5 females NOAEL: male: 870 mg/kg bw NOAEL: female: 862 mg/kg bw
Reliability	:	(1) valid without restriction

(2)

Type	:	Repeated dose
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	13 w
Frequency of treatm.	:	once daily
Post exposure period	:	1 w
Doses	:	0, 50, 150 or 450 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
Method	:	other: 30 rats/sex/dose, add.10 rats/sex for baseline clin. Pathol., interim kill at week 7, terminal kill at week 14, blood samples for hematology, clin.chemistry; urinalysis; gross and microsc. pathology; stat. anal.: Dunnett's t-t
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: purity: 98.6%
Result	:	signs of intoxication: 450 mg/kg bw, male, female: lethargy, tremors, hunched posture, dyspnea; >= 150 mg/kg bw: slight reduction in body weight gain of males 450 mg/kg: one high dose male was found dead on day 5 (cause not evident), reductions in weight gain for males and females; treatment-related gross and histomorphologic lesions not evident NOAEL: 50 mg/kg bw (male) NOAEL: 150 mg/kg (female)
Reliability	:	(2) valid with restrictions

(3)

Type	:	Repeated dose
Species	:	Rat
Sex	:	male/female

Strain	:	other: CD
Route of admin.	:	Gavage
Exposure period	:	13 w
Frequency of treatm.	:	Daily
Post exposure period	:	no data
Doses	:	50, 150 or 450 mg/kg bw/d in corn oil
Control group	:	yes, concurrent vehicle
LOAEL	:	ca. 50 mg/kg bw
Method	:	other: 10 rats/sex and group, observation of clinical signs, performance of neuro-behavioural test batteries, gross pathologic and histopathologic evaluation
Year	:	1986
GLP	:	no data
Test substance	:	other TS: no data on purity
Result	:	>= 50 mg/kg: salivation, hypoactivity, rapid laboured breathing 450 mg/kg: one female was found dead; increased closing of eyelids, pollakisuria (females), reduced food consumption; few significant changes in the performance of the neuro-behavioural test batteries (no further details reported); no brain weight changes, no gross or histopathological lesions in the brain or other nervous tissue

(4)

Type	:	Repeated dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	continuously in diet
Post exposure period	:	No
Doses	:	0, 300, 1000, 3000, 10000 or 30000 ppm (see remarks)
Control group	:	Yes
NOAEL	:	ca. 3000 ppm
Method	:	other: 5 mice/sex and dose, clinical observations twice daily, body weight initially, weekly and at termination, organ weights recorded and microscopically examined, statistical analysis
Year	:	1991
GLP	:	Yes
Test substance	:	other TS: purity > 98%
Remark	:	mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	53	66
1000 ppm	193	210
3000 ppm	521	651
10000 ppm	1730	2080
30000 ppm	4710	4940

Result	:	mortality: 0 ppm: 1/5 male; 10000 ppm: 1/5 females; 300000 ppm: 2/5 males, 2/5 females; Signs of toxicty: male, female; >= 100000 ppm: hunched posture, rough hair coat, laboured respiration (only

females), additionally at 30000 ppm: thin appearance, lethargy and tremor
relative liver weight increased: male from 3000 ppm, female from 300 ppm
relative kidney weight increased: male at 3000 ppm, female at 30000 ppm
histomorphology: female: 30000 ppm: mammary gland, ovarian and uterine atrophy

NOAEL (male): 521 mg/kg bw
NOAEL (female): 651 mg/kg bw

Reliability : (1) valid without restriction

(2)

Type : Repeated dose
Species : Mouse
Sex : Female
Strain : other: CBA/J
Route of admin. : Dermal
Exposure period : 6 w
Frequency of treatm. : 3 times/week
Post exposure period : 6 months
Doses : 0.5 % in acetone
Control group : Yes
Method : other: 5 rats, application of the substance to depilated or clipped lower back by mist spray; observation of the hair colour of the new hair regrowth were made weekly
Year : 1974
GLP : no data
Test substance : other TS: no data on purity

Result : No depigmentations of the regrowthed hair were observed.

(5)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Sister chromatid exchange assay
System of testing : human lymphocytes
Test concentration : 0 -1.0 Mm

Metabolic activation : no data
Result : Negative
Method : other: solvent: DMSO:EtOH (1:1), culture time 88-90 h
Year : 1986
GLP : no data
Test substance : other TS: purity: 99.2%

(6)

Type : Ames test
System of testing : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration : over a wide dose range (no further information) in DMSO
.
Metabolic activation : with and without

Result	:	Negative
Method	:	other: according to Ames, Proc.Natl.Acad.Sci.70, 2281(1973); Mutat.Res.31,347(1975); Nestmann, Cancer Res.39.4412(1979); Environ.Mutagen.1,361(1979)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: purity no data
Remark	:	presumbly negative, but solubility did not allow the testing of the compound in amounts that result in bacterial toxicity

(7)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537
Test concentration	:	no data
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: according to Ames, Mutation Res. 31, 347 (1975)
Year	:	1980
GLP	:	no data
Test substance	:	other TS: no data on purity

(8)

Type	:	Unscheduled DNA synthesis
System of testing	:	rat hepatocytes
Test concentration	:	502, 251, 100, 50.2, 25.1, 10.0, 5.02, 2.51, 1.0, 0.502 ug/ml in DMSO
Metabolic activation	:	With
Result	:	Negative
Method	:	other: according to Williams, Cancer Res. 37, 1845 (1977); Williams cited in deSerres (eds): Chemical Mutagens, Vol 8, pp.61, 1980, Plenum Press, NY
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: 99.8%
Remark	:	concentration range: 502 - 25.1 ug/ml: excessive toxicity
Reliability	:	(2) valid with restrictions

(9)

Type	:	Sister chromatid exchange assay
System of testing	:	human fibroblasts
Test concentration	:	0, 0.08, 0.8, 4 mM dissolved in ethanol; 8, 10, 30 mM dissolved in Eagle's Minimal Essential Medium (MEM)
Metabolic activation	:	Without
Result	:	Negative
Method	:	other: after add. of m-cresol incub. for 2h, then washing and add. of medium containing 15% fetal calf serum and BrdU for 48 h
Year	:	1984
GLP	:	no data
Test substance	:	other TS: purity: 99%

Remark : > 8 mM cytotoxic response
Reliability : (2) valid with restrictions

(10)

Type : other: DNA amplification
System of testing : SV40-transformed CHO cell
Test concentration : 5.0 mM in DMSO

Metabolic activation : Without
Result : Negative
Method : other: cells were incub. for 4d with m-cresol, then viability of the cells was determined, SV40-DNA content was detected by hybridization according to Lavi, Proc.Natl.Acad.Sci. (USA) 80,6144,1981; Winocour, Proc.Natl.Acad. Sci. (USA)77,48
Year : 1989
GLP : no data
Test substance : other TS: purity: 98%

(11)

Type : other: SV40 Mammilian Inductest
System of testing : Syrian hamster kidney cells (SV40)
Test concentration : 0.0001-0.0000001 ml

Metabolic activation : Without
Result : Positive
Method : Other
Year : 1983
GLP : No
Test substance : no data

Remark : Mammalian inductest

(12)

Type : Ames test
System of testing : Salmonella typhimurium TA 100, TA 1530, TA 1535, TA 1538,TA 1950, TA 1951, TA 1952, G 46
Test concentration : 0.5% in ethanol

Metabolic activation : no data
Result : Ambiguous
Method : other: according to Ames Mutat. Res. 31,347 (1975); Science 176, 47 (1972)
Year : 1975
GLP : no data
Test substance : other TS: no data on purity

Remark : a questionable effect was produced in the strain TA 1535

(13)

Type : other: SOS-Chromotest
System of testing : Escherichia coli PQ37
Test concentration : no data

Metabolic activation : Without

Result : Positive
Method : other: After termination of the nitrosation of m-cresol with ammonium sulphamate, test was performed according to Quillardet, Mutat. Res. 147,65 (1985)
Year : 1989
GLP : no data
Test substance : other TS: no data

(14)

Type : other: Prophage induction assay
System of testing : Escherichia coli / Bacteriophage lambda

Result : Positive

Remark : abstract only

(15)

Type : Cytogenetic assay
System of testing : Allium cepa

Metabolic activation : Without
Result : Negative

Year : 1948
GLP : No
Test substance : other TS: no data on purity

Remark : marginal effects

(16)

Type : Mouse lymphoma assay
System of testing : L 5178 Y (TK +/-) cells
Test concentration : 13.0 - 520 ug/ml in DMSO

Metabolic activation : with and without
Result : Negative
Method : other: preliminary cytotoxicity tests, procedure according to Clive, Mutation Res. 31,17,1975; Clive, Mutation Res. 59,61,1979, colony size not reported
Year : 1988
GLP : Yes
Test substance : other TS: 99.8%

Reliability : (2) valid with restrictions

(17)

Type : Cytogenetic assay
System of testing : Allium cepa

Test concentration	:	0, 0.015, 0.02 and 0.025% in destilled water
Metabolic activation	:	no data
Result	:	Positive
Method	:	other: treatment period: 0: 3 hrs; 0.015 24 hrs; 0.02: 5 hrs; 0.025: 5 hrs
Year	:	1965
GLP	:	No
Test substance	:	other TS: no data on purity

(18)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
Test concentration	:	0, 0.5, 5, 50,500, 5000 ug/plate dissolved in DMSO, highest dose toxic
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: plate incorporation assay according to Ames, Mutation Res. 31, 347 (1975)
Year	:	1982
GLP	:	no data
Test substance	:	other TS: purity: 98%
Reliability	:	(1) valid without restriction

(19)

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA98, TA 100, TA 1535, TA 1537
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31,347 (1975) and Yahagi, Cancer Lett. 1,91 (1975)<; to select dose range the chemical was checked for toxicity to S. typh. TA 100
Year	:	1983
GLP	:	no data
Test substance	:	other TS: 97%
Reliability	:	(1) valid without restriction

(20)

Type	:	Cytogenetic assay
System of testing	:	Chinese Hamster Ovary (CHO) cells
Test concentration	:	0, 198,297,398,495 ug/ml DMSO without; 0, 250, 500, 699, 749, 799, 898, 998, 999, 1100 ug/ml DMSO with S9-mix (>=898 ug/ml: toxic)
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: preliminary range finding studies; in accordance with OECD Guideline 473
Year	:	1988
GLP	:	yes
Test substance	:	other TS: purity: 99.8%

Reliability : (1) valid without restriction

(21)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Cytogenetic assay
Species : other: mouse bone marrow cells
Sex : male/female
Strain : ICR
Route of admin. : gavage
Exposure period : once
Doses : 0, 96, 320, 960 mg/kg bw in corn oil
Result : negative
Method : other: in accordance with OECD Guideline 475, 5 mice/sex/dose, bone marrow cells, sacrifice 6, 24, 48 hrs post treatment
Year : 1989
GLP : yes
Test substance : other TS: 99.8%

Remark : dose finding study: see chapter 5.1
Reliability : (1) valid without restriction

(22)

Type : Sister chromatid exchange assay
Species : mouse
Sex : male
Strain : DBA
Route of admin. : i.p.
Exposure period : single application
Doses : 0, 200 mg/kg bw dissolved in sunflower oil
Result : negative
Method : other: 3/4 mice were partly hepatectomized 5 d prior to exposure, 0.5h later BrdU tablets were implanted s.c.; 17h later single i.p. inj. of colchicine, 4h later sacrifice: bone marrow cells, alv. macrophages, regen. liver cells
Year : 1984
GLP : no data
Test substance : other TS: purity. 99%

Result : No increase in SCE frequencies in the intact mice as well as in the partially hepatectomized mice.

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species : rat
Sex : female
Strain : Sprague-Dawley
Route of admin. : gavage
Exposure period : day 6 through day 15 of gestation
Frequency of treatm. : daily
Duration of test : until gd 21

Doses	:	0, 30, 175 or 450 mg/kg bw/d
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	ca. 175 mg/kg bw
NOAEL teratogen.	:	ca. 450 mg/kg bw
Method	:	other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year	:	1988
GLP	:	yes
Test substance	:	other TS: purity: 99.4%
Result	:	450 mg/kg: significant maternal toxicity (reduced food intake, reduced maternal body weights and weight gain during dosing period; reduced gestational weight gain (day 0-21); clinical signs of toxicity: hypoactivity, ataxia, tremors, audible respiration, perioral wetness; increased relative liver weights) no embryotoxicity or teratogenicity was observed at any dosage level
Reliability	:	(1) valid without restriction

(23)

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	gavage
Exposure period	:	day 6 through day 18 of gestation
Frequency of treatm.	:	once daily
Duration of test	:	until day 29 of gestation
Doses	:	0, 50, 150, 300 or 500 mg/kg bw/d
Control group	:	yes
Remark	:	8 rabbits/dose range-finding study
Result	:	50 mg/kg: one doe aborted; ataxia, twitching, gasping, audible, labored and rapid respiration; increased relative liver weights 150 mg/kg: maternal mortality 2/8; reduced food consumption on gd 7-9; significantly depressed body weight gain for gd 6-12; cleft palace in 1 fetus >= 300 mg/kg: reduced food consumption on gd 6-10; significantly elevated clinicals signs of toxicity (CNS and cardiopulmonary categories; see at 50 mg/kg) 300 mg/kg: maternal mortality 1/8; one doe aborted; reduced body weight on gd 12 and significantly depressed body weight gain on gd 6-12; increased preimplantation loss and increase in dead fetuses/litter; forelimb and pectoral girdle anomalies in 4 fetuses in 2 litters; cleft palate in 1 fetus; small tongue 500 mg/kg: maternal mortality 8/8

(24)

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	gavage
Exposure period	:	day 6 through day 18 of gestation
Frequency of treatm.	:	once daily
Duration of test	:	until day 29 of gestation
Doses	:	0, 5, 50 or 100 mg/kg bw/day
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	ca. 5 mg/kg bw
NOAEL teratogen.	:	ca. 100 mg/kg bw
Method	:	other: following the TSCA Health Effects Test guidelines for Specific Organ/Tissue Toxicity - Developmental Toxicity (EPA, 1984,1987)
Year	:	1988
GLP	:	yes
Test substance	:	other TS: purity: 99.7%
Result	:	>= 50 mg/kg: audible respiration and ocular discharge No embryotoxicity or teratogenicity was observed at any dosage employed.
Reliability	:	(1) valid without restriction

(25)

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	s.c.
Exposure period	:	day 7 through day 17 of gestation
Frequency of treatm.	:	daily
Duration of test	:	until post partum
Doses	:	90 mg/kg bw/d (30 ml/kg bw 0.3%)
Control group	:	yes
Result	:	m-cresol was used as the solvent at a concentration of 0.3%; no negative effects on F0- or F1-generation were observed when compared with control animals.

(26)

Species	:	rat
Sex	:	female
Strain	:	Wistar
Route of admin.	:	s.c.
Exposure period	:	day 17 of gestation until 21 days after birth
Frequency of treatm.	:	daily
Duration of test	:	until 8 w post partum
Doses	:	90 mg/kg bw/d (30 mg/kg 0.3%)
Control group	:	yes
Result	:	m-cresol was used as the solvent at a concentration of 0.3%; no negative effects on F0-, F1- or F2-generation were observed when compared with controls (no fetotoxicity, normal postnatal development, normal behaviour and fertility).

(27)

Species	:	mouse
Sex	:	female
Strain	:	other: ICR-SLC
Route of admin.	:	s.c.
Exposure period	:	day 6 through day 15 of gestation
Frequency of treatm.	:	daily
Duration of test	:	until 5 w post partum
Doses	:	no data
Control group	:	yes

Result : m-cresol was used as the solvent; no signs of fetotoxicity or teratogenicity, no maternal toxicity.

(28)

Species	:	rabbit
Sex	:	female
Strain	:	no data
Route of admin.	:	s.c.
Exposure period	:	day 6 through day 18 of gestation
Frequency of treatm.	:	daily
Duration of test	:	until >= 12 d after exposure
Doses	:	30 mg/kg bw/d (10 ml/kg 0.3%)
Control group	:	Yes

Result : m-cresol was used as the solvent at a concentration of 0.3%; decreased maternal food consumption and body weight gain after day 14 of gestation, increased average number of implantations and reduced mean body weights in male fetuses, no increase of anomalies.

(29)

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APPENDIX B
ROBUST SUMMARY FOR p-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

REPEATED DOSE TOXICITY

Type	:	Repeat dose
Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	83 - 87 mg/kg bw
LOAEL	:	242 - 256 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	other TS: purity > 98%

Remark :

Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	25	25
1000 ppm	87	83
3000 ppm	256	242
10000 ppm	835	769
30000 ppm	2180	2060

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result :

There were no deaths. Decreased mean final body weights, body weight gains and feed consumption occurred in both the top-dose males and females. These animals also showed clinical signs of toxicity, including hunched posture and rough hair coat.
Increased relative liver and kidney weights were recorded in females fed >/= 242 mg/kg bw/day or 2060 mg/kg bw/day, respectively and in males fed >/= 835 mg/kg bw/day. No

gross lesions were noted at necropsy.
Histopathological evaluation revealed effects in the uterus in the top-dose females; in the nasal cavity in both males and females at >/= 256 and >/= 242 mg/kg bw/day, respectively; and bone marrow in both males and females at >/= 256 and >/= 769 mg/kg bw/day, respectively.

Reliability : (1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	50 - 60 mg/kg bw
LOAEL	:	60 - 163 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	other TS: purity > 98%

Remark : Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination.

mean compound consumption (mg/kg bw/day):

	males	females
0 ppm	0	0
300 ppm	50	60
1000 ppm	163	207
3000 ppm	469	564
10000 ppm	1410	1590

Consumption data for the top dose were not calculated due to 100% mortality at this level.

At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.

Result : There was 100% mortality at the highest dose level. One male receiving 1410 mg/kg bw/day also died. Mean final body weights and mean body weight gains for surviving males at 1410 mg/kg bw/day were significantly lower than in the control groups; feed consumption was depressed at the beginning of the study in males at 1410 mg/kg bw/day and in females at 1590 mg/kg bw/day. Clinical signs of toxicity included hunched posture, rough

hair coat, lethargy, and hypothermia in the top-dose females that died and, together with laboured breathing and paleness, in the males fed >/= 1410 mg/kg bw/day.
Relative liver weight was increased in females receiving >/= 564 mg/kg bw/day; in males, the relative liver and heart weights were increased at 1410 mg/kg bw/day and relative kidney weight at >/= 469 mg/kg bw/day. No gross lesions were noted at necropsy.
Histopathological evaluation revealed nasal lesions in the females at all doses and in males at >/= 163 mg/kg bw/day. In the top-dose animals which died, renal and hepatic necrosis and bone marrow hypocellularity was noted.

Reliability : (1) valid without restriction

(1)

Type : Repeat dose
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : Gavage
Exposure period : 13 weeks
Frequency of treatm. : 7 days/week

Doses : 0, 50, 175, 600 mg/kg bw/day
Control group : Yes
LOAEL : 50 mg/kg bw
Method : other
Year :
GLP : no data
Test substance : no data

Remark : Groups of 30 rats/sex were administered p-cresol in corn oil. The original data are unpublished and are available from the US EPA Freedom of Information Office. No further experimental details are available from the citing reviews (ATSDR, 1990; IPCS, 1993).

Result : 600 mg/kg: There was some mortality. Overt signs of toxicity at this dose included lethargy, tremors, convulsions and coma. There was also a decrease in the body weight gains. In females, increased serum enzyme levels were observed, which were correlated with the presence of hepatic inflammation, and serum cholesterol. The relative heart and liver weights of males were increased and their absolute brain weight decreased. Females showed decreased absolute brain and ovary weights. Microscopic examination revealed a small increased incidence of epithelial metaplasia of the trachea in both sexes.
>/= 175 mg/kg: serum protein levels and relative kidney weight were increased in the males and blood effects (decreased red blood cell count and haemoglobin and haematocrit values) observed in the females.
A small increase in the incidence of nephropathy, which did not appear to be dose-related, was seen in the males at all dose levels.

Reliability : (2) valid with restrictions

(2)

GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, 100, 1535, 1537.
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31, 347 (1975) and Yahagi, Cancer Lett. 1, 91 (1975; to select dose range the chemical was checked for toxicity to S. typh. TA100
Year	:	1983
GLP	:	no data
Test substance	:	other TS: purity >97%
Remark	:	This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability	:	(1) valid without restriction

(3)

Type	:	Cytogenetic assay
System of testing	:	Chinese hamster ovary cells
Test concentration	:	30 to 902 ug/ml
Metabolic activation	:	with and without
Result	:	Positive
Method	:	other: similar to OECD Guideline 473
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Method	:	Duplicate CHO cultures were incubated with 15-301 ug/ml of the test substance in the nonactivation aberrations assay. The metabolic activation cultures were treated with 30-300 ug/ml of the test substance in a 10 hour assay and with 301-902 ug/ml in a 20 hour assay.
Result	:	Increases in chromosomally aberrant cells were observed in the nonactivation assay at all doses. Increases in the chromosomally aberrant cells were observed in the 20 hour assay with metabolic activation at 301 and 601 ug/ml.
Reliability	:	(1) valid without restriction

(4)

Type	:	other: cell transformation assay
System of testing	:	mouse BALB/c-3T3 cells
Test concentration	:	0.81 nl/ml, 3.25 nl/ml, 5 nl/ml, 10 nl/ml, and 15 nl/ml
Cycotoxic concentr.	:	31.3 nl/ml
Metabolic activation	:	Without
Result	:	Positive
Method	:	EPA OTS 795.2850
Year	:	1988

GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Reliability	:	(1) valid without restriction

(5)

Type	:	Mouse lymphoma assay
System of testing	:	L5178Y mouse lymphoma cells
Test concentration	:	with activation: 0.256 ug/ml, 0.511 ug/ml, 0.767 ug/ml, 1.02 ug/ml, 1.53 ug/ml, and 3.07 ug/ml. without activation: 51.1 ug/ml, 102 ug/ml, 153 ug/ml, 204 ug/ml, 307 ug/l, and 409 ug/ml.
Cycotoxic concentr.	:	with activation: 5.11 ug/ml. without activation: 511 ug/ml.
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: similar to OECD Guideline 476
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Reliability	:	(1) valid without restriction

(6)

Type	:	DNA damage and repair assay
System of testing	:	human lymphocytes
Test concentration	:	5 x 10-6 - 25 x 10-6 M
Metabolic activation	:	Without
Result	:	Positive
Method	:	Other
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-cresol, purity not noted
Method	:	p-Cresol was tested for its ability to inhibit semiconservative DNA synthesis. Initially, DNA repair was induced by irradiation and, in these cells, semiconservative DNA synthesis was blocked by treatment with with hydroxyurea. In both studies, cells were treated with radiolabelled thymidine for 2 hours and incorporation of thymidine into the cells was measured.
Result	:	p-Cresol inhibited both UV-induced DNA repair synthesis and semiconservative DNA synthesis as seen by a reduction in radiolabelled thymidine incorporation. It was unclear from the report if this inhibition was seen at all concentrations tested but at the top dose, 21% inhibition of DNA repair synthesis and 25% inhibition of semiconservative DNA synthesis was found.

(7)

Type	:	Sister chromatid exchange assay
System of testing	:	human lymohocytes
Test concentration	:	0 - 0.5 Mm
Metabolic activation	:	no data

Result	:	Negative
Method	:	Other
Year	:	1986
GLP	:	no data
Test substance	:	other TS: p-cresol, 99.9% purity
Remark	:	Styrene-7,8-oxide acted as the positive control. Cells were incubated with p-cresol for 88-90 hr before being analysed. This endpoint had been studied by another investigator and reported results similar to the study mentioned above.

(8) (9)

Type	:	Ames test
System of testing	:	Salmonella typhimurium strains TA98, 100, 1535, 1537, TA1538
Test concentration	:	0, 0.5, 5, 50, 500, 5000 ug/plate dissolved in DMSO, highest dose cytotoxic
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutation Res. 31, 347 (1975)
Year	:	1975
GLP	:	no data
Test substance	:	other TS: purity : 98%
Reliability	:	(1) valid without restriction

(10)

GENETIC TOXICITY 'IN VIVO'

Type	:	Dominant lethal assay
Species	:	Mouse
Sex	:	male/female
Strain	:	ICR
Route of admin.	:	Gavage
Exposure period	:	Single dose
Doses	:	0, 100, 275, and 550 mg/kg
Result	:	Negative
Method	:	EPA OTS 798.5450
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Reliability	:	(1) valid without restriction

(11)

Type	:	Drosophila SLRL test
Species	:	Drosophila melanogaster
Sex	:	Male
Strain	:	other: Oregon-R
Route of admin.	:	oral feed
Exposure period	:	3 days

Doses	:	0, 60, 300 and 600 ug/ml 5% sucrose
Result	:	Negative
Method	:	EPA OTS 798.5275
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 99.8% purity
Reliability	:	(1) valid without restriction

(12)

Type	:	Sister chromatid exchange assay
Species	:	Mouse
Sex	:	Male
Strain	:	DBA
Route of admin.	:	i.p.
Exposure period	:	single dose
Doses	:	0, 75 mg/kg bw in sunflower oil
Result	:	Negative
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	other TS: p-cresol, purity >99%; obtained from Aldrich Chemical Co.
Method	:	p-Cresol was administered to 2 or 3 intact or hepatectomized male mice by single intraperitoneal injection. Negative and positive controls received 0.35 ml sunflower oil (4 intact and 5 hepatectomized animals) and 5 mg cyclophosphamide/kg bw (2 intact animals), respectively. After 30 min, DNA labelling was initiated using BrdU. After a further 21 hr the animals were killed, cells isolated and harvested and sister chromatid exchange (SCE) frequency in bone marrow cells, alveolar macrophages and regenerating liver cells analysed. Some of the mice were partially hepatectomized to induce liver cell regeneration.
Result	:	p-Cresol did not induce significant increases in SCE frequencies in any of the cell types examined. The doses tested were overtly toxic to the mice, causing lethargy, piloerection and lacrimation.
Reliability	:	(2) valid with restrictions

(13)

TOXICITY TO FERTILITY

Type	:	Two generation study
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	see remarks
Frequency of treatm.	:	5 days per week
Premating exposure period		

Male	:	10 weeks
Female	:	10 weeks
Duration of test	:	see remarks
No. of generation studies	:	2
Doses	:	0, 30, 175, 450 mg/kg bw/day; 25 rats/sex/group
Control group	:	yes, concurrent vehicle
NOAEL parental	:	ca. 30 mg/kg bw
NOAEL F1 offspring	:	ca. 175 mg/kg bw
NOAEL F2 offspring	:	ca. 175 mg/kg bw
other: NOAEL (fertility)	:	ca. 450 mg/kg bw
Method	:	EPA OPP 83-4
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 98.93% pure
Remark	:	Groups of rats were administered p-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.
Result	:	Clinical signs of toxicity occurred in F0 and F1 males and females at 450 mg/kg bw/day and included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perinasal encrustation (not in F0 males), and perioral wetness occurred at >= 175 mg/kg bw. No reproductive parameters were effected in either of the two generations (F1 or F2). p-Cresol caused increased still births in the F1 and F2 generations: in F1 pups at 175 (but not 450) mg/kg/day and in F2 pups at 30 and 450 (but not 175) mg/kg/day. There was some variability in the number of stillborn in control groups in F1 and F2 generation (2 versus 0) and there was no clear dose-dependent effect in both generations (control/low/mid/high dose: F1 pups: 2/4/13/6; F2 pups: 0/7/4/9). In F2 (but not F1) live birth indices were reduced at 30 and 450 (not 175) mg/kg/day. Without any other effects especially in the 30 mg/kg bw-group it is unclear whether the effects on live birth indices were substance related. Pup survival indices in both generations were not affected by treatment.
Reliability	:	(1) valid without restriction

(14)

DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	days 6 – 15

Frequency of treatm.	**:**	Daily
Duration of test	**:**	10 days
Doses	**:**	0, 30, 175, 450 mg/kg bw/day; 25 inseminated females/group
Control group	**:**	yes, concurrent vehicle
NOAEL maternal tox.	**:**	= 175 mg/kg bw
NOAEL teratogen.	**:**	= 175 mg/kg bw
Method	**:**	EPA OPP 83-3
Year	**:**	1988
GLP	**:**	Yes
Test substance	**:**	Other TS: p-cresol. purity = 98.93%
Remark	**:**	p-Cresol was administered in corn oil.
Result	**:**	Maternal toxicity occurred at 450 mg/kg bw/day and included death, decreased food consumption and body weight gain, audible respiration, hypoactivity, ataxia and tremors. p-Cresol caused mild fetotoxicity at the 450 mg/kg, as seen by reduced ossification in three skeletal districts. In addition, fetal body weight was reduced at the 450 mg/kg dose level. There was no treatment-related increased incidence of malformations at any dosage.
Reliability	**:**	(1) valid without restriction

(15)

Species	**:**	Rabbit
Sex	**:**	Female
Strain	**:**	New Zealand white
Route of admin.	**:**	Gavage
Exposure period	**:**	Days 6 - 18 of gestation
Frequency of treatm.	**:**	Daily
Duration of test	**:**	24 days
Doses	**:**	0, 5, 50, 100 mg/kg bw/day; 14 inseminated females/group
Control group	**:**	yes, concurrent vehicle
NOAEL maternal tox.	**:**	< 50 mg/kg bw
NOAEL teratogen.	**:**	= 100 mg/kg bw
Method	**:**	EPA OPP 83-3
Year	**:**	1988
GLP	**:**	Yes
Test substance	**:**	Other TS: p-cresol. purity = 98.93%
Remark	**:**	p-Cresol was administered in corn oil.
Result	**:**	Maternal toxicity including audible respiration, ocular discharge, hypoactivity and death were seen at 50 mg/kg bw/day or above. p-Cresol had no effects on the developing embryos at any of the doses tested.
Reliability	**:**	(1) valid without restriction

(15)

Species	**:**	Rat
Sex	**:**	Male/female
Strain	**:**	Sprague-Dawley
Route of admin.	**:**	Gavage
Exposure period	**:**	10 weeks prior to mating through life
Frequency of treatm.	**:**	Daily
Duration of test	**:**	Lifelong
Doses	**:**	0, 30, 175, 450 mg/kg bw/day; 25 animals/sex/group

Control group	**:**	yes, concurrent vehicle
NOAEL maternal tox.	**:**	= 175 mg/kg bw
NOAEL teratogen.	**:**	= 175 mg/kg bw
Method	**:**	Other: EPA OPP 83-4
Year	**:**	1989
GLP	**:**	Yes
Test substance	**:**	Other TS: p-cresol, purity >98%
Remark	**:**	Developmental endpoints were also monitored in the 2-generation reproduction studies in rats discussed previously. Groups of rats were administered p-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.
Result	**:**	p-Cresols caused effects on pup bodyweight at some time during development when given at 450 mg/kg bw/day; a dose causing overt parental toxicity. Occasional bodyweight changes were seen at lower doses but it is not clear if these were treatment-related.
Reliability	**:**	(1) valid without restriction

(14)

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APPENDIX C
ROBUST SUMMARY FOR o-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

REPEATED DOSE TOXICITY

Type	:	Repeat dose
Species	:	Rat
Sex	:	Male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	83-87 mg/kg bw
LOAEL	:	242-256 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	other TS: purity > 98%
Remark	:	Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no deaths. Decreased mean final body weights in high-dose females; body weight gains and feed consumption occurred in both the top-dose males and females. Increased liver and kidney weights were recorded in the top two dose groups. Relative liver and kidney weights were increased in the top three and top two dose groups for males and females, respectively. No gross or histopathologic lesions were noted at necropsy.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1

Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	50-60 mg/kg bw
LOAEL	:	60-163 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	other TS: purity > 98%
Remark	:	Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	Mean final body weights and mean body weight gains reduced for males at top two dose groups; feed consumption was depressed at the beginning of the study in males top two dose levels. Clinical signs of toxicity, including hunched posture, rough hair coat and lethargy, were noted in high-dose animals. Hypothermia, rapid breathing and tremors were noted in the top-dose males. Relative liver weight was increased in the three highest dose groups. Relative kidney weights were increased in high-dose females. No gross lesions were noted at necropsy. Histopathological evaluation revealed ovarian atrophy in the high dose and uterine atrophy in the top dose levels.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	13 weeks
Frequency of treatm.	:	7 days/week
Doses	:	0, 50, 175, 600 mg/kg bw/day
Control group	:	Yes
LOAEL	:	50 mg/kg bw
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data

Remark	:	Groups of 30 rats/sex were administered p-cresol in corn oil. The original data are unpublished and are available from the US EPA Freedom of Information Office. No further experimental details are available from the citing reviews (ATSDR, 1990; IPCS, 1993).
Result	:	600 mg/kg: Mortality in 19/30 females and 9/30 males. Overt signs of toxicity at this dose included CNS depresion, lethargy, tremors, and convulsions occurring within one hour post-dosing but not beyond one hour post-dosing. High-dose male body weight gain suppression. No effects on clinical chemistry, hematology, urinalysis, no treatment-related ophthalmic lesions, no effect on organ weights, no treatment-related gross or microscopic lesions.
Reliability	:	(2) valid with restrictions

(2)

Type	:	Repeat dose
Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	Ad libitum
Post exposure period	:	None
Doses	:	0, 1880, 3750, 7500, 15000 9r 30000 ppm
Control group	:	yes, concurrent no treatment
LOAEL	:	7500 ppm (relative and absolute liver weight)
NOAEL	:	15000 ppm
Year	:	1992
GLP	:	No
Test substance	:	other TS: purity > 98%
Remark	:	Groups of 20 rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no deaths. Decreased mean final body weights in high-dose males; body weight gains and feed consumption occurred in both males and females of the top two doses. Increased liver and kidney weights were recorded in the top two dose groups (three dose groups for liver weight). Relative testes weight was increased in high-dose males and relative thymus weight was increased in males of the top two dose groups. There was evidence of increased bone marrow hypocellularity in males of the top dose and females of the top two doses.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	Ad libitum
Post exposure period	:	None
Doses	:	0, 1250, 2500, 5000, 10000 or 20000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	2500 ppm (female body weight)
LOAEL	:	5000 ppm
	:	
Year	:	1992
GLP	:	No
Test substance	:	other TS: purity > 98%
Remark	:	Groups of 10 mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	Mean final body weights and mean body weight gains reduced for males at the top dose and females of the top three dose groups; feed consumption was depressed at the beginning of the study in the high-dose groups. Clinical signs of toxicity included hunched posture, rough hair coat were noted in high-dose male animals. All male dose groups and females of the three highest dose groups had relative liver weight increases. Relative kidney weights were increased in high-dose females. High-dose males had increased relative testes weight. Relative thymus weight was increased in high-dose animals. Histopathological evaluation revealed minimal forestomach atrophy in the high dose groups.
Reliability	:	(1) valid without restriction

(1)

GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 98, 100, 1535, 1537.
Test concentration	:	0.0, 3.3, 10.0, 33.0, 100.0, 333.0 ug/plate in water as solvent
Metabolic activation	:	with and without
Result	:	Negative
Method	:	other: preincubation methodology according to Ames, Mutat. Res. 31, 347 (1975) and Yahagi, Cancer Lett. 1, 91 (1975); to select dose range the chemical was checked for toxicity to S. typh. TA100
Year	:	1983
GLP	:	no data
Test substance	:	other TS: purity >97%
Remark	:	This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability	:	(1) valid without restriction

(3)

Type	:	Cytogenetic assay
System of testing	:	Chinese hamster ovary cells
Test concentration	:	30 to 902 ug/ml
Cycotoxic concentr.	:	
Metabolic activation	:	with and without
Result	:	Positive
Method	:	other: similar to OECD Guideline 473
GLP	:	Yes
Test substance	:	other TS: 99.8% pure
Method	:	Duplicate CHO cultures were incubated with 15-301 ug/ml of the test substance in the nonactivation aberrations assay. The metabolic activation cultures were treated with 30-300 ug/ml of the test substance in a 10 hour assay and with 301-902 ug/ml in a 20 hour assay.
Result	:	Increases in chromosomally aberrant cells were observed in the nonactivation assay at all doses. Increases in the chromosomally aberrant cells were observed in the 20 hour assay with metabolic activation at 301 and 601 ug/ml.
Reliability	:	(1) valid without restriction

(4)

Type	:	other: cell transformation assay
System of testing	:	mouse BALB/c-3T3 cells
Test concentration	:	0.81 nl/ml, 3.25 nl/ml, 5 nl/ml, 10 nl/ml, and 15 nl/ml
Cycotoxic concentr.	:	31.3 nl/ml
Metabolic activation	:	Without
Result	:	Positive
Method	:	EPA OTS 795.2850
Year	:	1988
GLP	:	Yes
Test substance	:	other TS: 99.8% pure

Reliability : (1) valid without restriction

(5)

Type : Mouse lymphoma assay
System of testing : L5178Y mouse lymphoma cells

Metabolic activation : with and without
Result : Negative
Method : other: similar to OECD Guide-line 476
Year : 1988
GLP : Yes
Test substance : other TS: 99.8% pure

Reliability : (1) valid without restriction

(6)

Type : DNA damage and repair assay
System of testing : E. coli

Metabolic activation : With and without
Result : Negative
Method : Other
Year : 1980
GLP : no data
Test substance : other TS: o-cresol, purity not noted
Flag : Critical study for SIDS endpoint

(7)

Type : Sister chromatid exchange assay
System of testing : human lymohocytes
Test concentration : 0 - 0.5 Mm

Metabolic activation : no data
Result : Negative, Equivocal
Method : Other
Year : 1986
GLP : no data
Test substance : other TS: o-cresol, 99.9% purity

Remark : Styrene-7,8-oxide acted as the positive control. Cells were incubated with p-cresol for 88-90 hr before being analysed.
This endpoint had been studied by another investigator and reported results similar to the study mentioned above.

(8) (9)

Type : Unscheduled DNA Synthesis
System of testing : Rat hepatocytesi

Result : Negative

Method : Other
Year : 1981
GLP : no data
Test substance : other TS: o-cresol, purity not noted

(10)

Type : *In Vitro* Cell Transformation
System of testing : BALB 3T3

Result : **Negative**

Year : **1981**
GLP : **No data**
Test substance : **o-cresol**

(11)

GENETIC TOXICITY 'IN VIVO'

Type : Dominant lethal assay
Species : Mouse
Sex : male/female
Strain : ICR
Route of admin. : Gavage
Exposure period : Single dose
Doses : 0, 75, 250, and 750 mg/kg
Result : Negative
Method : EPA OTS 798.5450
Year : 1989
GLP : Yes
Test substance : other TS: 99.8% pure

Reliability : (1) valid without restriction

(12)

Type : Drosophila SLRL test
Species : Drosophila melanogaster
Sex : Male
Strain : other: Oregon-R
Route of admin. : oral feed
Exposure period : 3 days
Doses : 0, 100, 500 and 1000 ug/ml 5% sucrose
Result : Negative
Method : EPA OTS 798.5275
Year : 1989
GLP : Yes
Test substance : Other TS: 99.8% purity

Reliability : (1) valid without restriction

TOXICITY TO FERTILITY

Type	:	Two generation study
Species	:	Rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	see remarks
Frequency of treatm.	:	5 days per week
Premating exposure period		
Male	:	10 weeks
Female	:	10 weeks
Duration of test	:	see remarks
No. of generation studies	:	
Doses	:	0, 30, 175, 450 mg/kg bw/day; 25 rats/sex/group
Control group	:	yes, concurrent vehicle
NOAEL parental	:	ca. 30 mg/kg bw
NOAEL F1 offspring	:	ca. 175 mg/kg bw
NOAEL F2 offspring	:	ca. 175 mg/kg bw
other: NOAEL (fertility)	:	ca. 450 mg/kg bw
Method	:	EPA OPP 83-4
Year	:	1989
GLP	:	Yes
Test substance	:	other TS: 98.93% pure

Remark : Groups of rats were administered o-cresol in corn oil. Exposure began 10 weeks prior to breeding and continued in the females throughout mating, gestation and lactation. The offspring were gavaged with the same doses as their respective parents for 11 weeks; the females again being dosed throughout mating, gestation and lactation. The F2 offspring were sacrificed at weaning.

Result : Clinical signs of toxicity occurred in F0 and F1 males and females at 450 mg/kg bw/day and included hypoactivity, ataxia, twitches, tremors, prostration, urine stains, audible respiration, perinasal encrustation (not in F0 males), and perioral wetness occurred at >= 175 mg/kg bw.

No reproductive parameters were effected in either of the two generations (F1 or F2).
o-Cresol caused increased still births in the F1 and F2 generations: in F1 pups at 175 (but not 450) mg/kg/day and in F2 pups at 30 and 450 (but not 175) mg/kg/day. There was some variability in the number of stillborn in control groups in F1 and F2 generation (2 versus 0) and there was no clear dose-dependent effect in both generations (control/low/mid/high dose: F1 pups: 2/4/13/6; F2 pups: 0/7/4/9). In F2 (but not F1) live birth indices were reduced at 30 and 450 (not 175) mg/kg/day. Without any other effects especially in the 30 mg/kg bw-group it is unclear whether the effects on live birth indices were substance related. Pup survival indices in both generations were not

affected by treatment.

Reliability : (1) valid without restriction

(14)

DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat
Sex	:	Female
Strain	:	Sprague-Dawley
Route of admin.	:	Gavage
Exposure period	:	days 6-15
Frequency of treatm.	:	Daily
Duration of test	:	10 days
Doses	:	0, 30, 175, 450 mg/kg bw/day; 25 inseminated females/group
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	= 175 mg/kg bw
NOAEL teratogen.	:	= 175 mg/kg bw
Method	:	EPA OPP 83-3
Year	:	1988
GLP	:	Yes
Test substance	:	Other TS: o-cresol, purity = 98.93%
Remark	:	o-Cresol was administered in corn oil.
Result	:	Maternal toxicity occurred at 450 mg/kg bw/day and included death, decreased food consumption and body weight gain, audible respiration, hypoactivity, ataxia and tremors. There was no treatment-related increased incidence of malformations at any dosage.
Reliability	:	(1) valid without restriction

(15)

Species	:	Rabbit
Sex	:	Female
Strain	:	New Zealand white
Route of admin.	:	Gavage
Exposure period	:	Days 6-18 of gestation
Frequency of treatm.	:	Daily
Duration of test	:	24 days
Doses	:	0, 5, 50, 100 mg/kg bw/day; 14 inseminated females/group
Control group	:	yes, concurrent vehicle
NOAEL maternal tox.	:	5 mg/kg bw
NOAEL developmental	:	50 mg/kg bw
Method	:	EPA OPP 83-3
Year	:	1988
GLP	:	Yes
Test substance	:	Other TS: o-cresol, purity = 98.93%
Remark	:	o-Cresol was administered in corn oil.
Result	:	Maternal toxicity including audible respiration, ocular discharge were seen at 50 mg/kg bw/day or above. o-Cresol had no effects on the developing embryos at any of the doses tested.
Reliability	:	(1) valid without restriction

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APPENDIX D
ROBUST SUMMARY FOR MIXED CRESOL ISOMERS TOXICITY STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

REPEATED DOSE TOXICITY

Type	:	Repeat dose
Species	:	Rat
Sex	:	Male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	300 ppm
LOAEL	:	1000 ppm nasal respiratory hyperplasia in females
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of five rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no deaths. Decreased mean final body weights in high-dose males; body weight gains and feed consumption occurred in both the top-dose males and females. Increased relative kidney weights were recorded in the top two dose groups of each sex. Relative liver weights were increased in the top three and top four dose groups for males and females, respectively. High-dose males had an increased relative testes weight. No gross lesions were noted at necropsy. Hyperplasia of the respiratory , epithelium of the nasal cavity was observed in the top three dose levels, both sexes. Mild-to-moderate bone marrow hypoplasia was seen in the top three male dose groups and the top two female dose groups. Minimal-to-mild esophagus and forestomach hyperplasia was reported for males and females of the top three dose groups.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	28 days
Frequency of treatm.	:	ad libitum
Post exposure period	:	None
Doses	:	0, 300, 1000, 3000, 10000, 30000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	50-60 mg/kg bw
LOAEL	:	60-163 mg/kg bw
Method	:	EPA OTS 795.2600
Year	:	1992
GLP	:	Yes
Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of five mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no unschedule deaths in the study. Mean final body weights and mean body weight gains were reduced for high-dose males and females. Body weight gain was suppressed in the top three dose groups of males. Feed consumption was depressed at the beginning of the study. Clinical signs of toxicity in high-dose animals were: alopecia, dehydration, hunched posture, rough hair coat, hypothgermia and lethargy. Relative liver weight was increased in the four highest dose groups of males and the three highest dose groups of females. High-dose males had a relative increase in testes weight. High-dose fermales had increased relative kidney weights. No gross lesions were noted at necropsy. Histopathological evaluation revealed epithelial hyperplasia of varying degrees throughout the respiratory tract.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	Ad libitum

Post exposure period	:	None
Doses	:	0, 1880, 3750, 7500, 15000 or 30000 ppm
Control group	:	yes, concurrent no treatment
LOAEL	:	7500 ppm (relative and absolute liver weight)
NOAEL	:	15000 ppm
Year	:	1992
GLP	:	No
Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of 20 rats/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no deaths. Decreased mean final body weights in the two highest-dose males and female groups; feed consumption suppressed in high-dose groups of both sexes in first week of study. Increased relative kidney weights were recorded in the top three male dose groups and the top female dose group. Relative liver weight was elevated for animals of the top three dose groups. Relative testes weight was increased in the top two male dose groups. There was dose-related evidence of hyperplasia of the nasal respiratory epithelium. Thyroid follicle changes (increased colloid formation) was reported for males and females in a dose-related manner. Minimal increased bone marrow hypocellularity was reported for males of the top dose and females of the top dose group. Minimal-to-mild uterine atrophy was reported for the two top dose groups.
Reliability	:	(1) valid without restriction

(1)

Type	:	Repeat dose
Species	:	Mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	oral feed
Exposure period	:	90 days
Frequency of treatm.	:	Ad libitum
Post exposure period	:	None
Doses	:	0, 625, 1250, 2500, 5000, 10000 ppm
Control group	:	yes, concurrent no treatment
NOAEL	:	2500 ppm (female body weight)
LOAEL	:	5000 ppm
Year	:	1992
GLP	:	No

Test substance	:	m/p-cresol, 60%-40% mix TS: purity > 98%
Remark	:	Groups of 10 mice/sex/dose were tested. Feed consumption was recorded twice weekly, the rats were observed for signs of toxicity twice daily and weighed at study initiation, weekly and at study termination. At necropsy, the brain, heart, right kidney, liver, lungs, thymus and right testis were weighed in all animals. Complete histopathological examination was made on all controls, all animals in the highest dose group with at least 60% survivors at study termination and all animals in the higher dose groups, inclusive of early deaths. For the lower dosed animals, target organs and gross lesions were examined.
Result	:	There were no unscheduled deaths during the study. Mean final body weights and mean body weight gain (males) were reduced for high-dose animals; feed consumption was slightly depressed in the high-dose groups. Male dose groups (top two dose groups) and females of the highest dose groups had relative liver weight increases. There were no liver lesions reported from microscopic examination. Histopathological evaluation revealed hyperplasia of the nasal respiratory epithelium.
Reliability	:	(1) valid without restriction

(1)

GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	Salmonella typhimurium TA 97, TA 98, 100, 1535.
Test concentration	:	0.0, 10.0, 33.0, 100.0, 333.0, 1000 and 3333 or 6666 ug/plate
Metabolic activation	:	with and without hamster and rat S-9
Result	:	Negative
Method	:	Method of Zeiger, et al., 1988.
Year	:	1990
GLP	:	no data
Test substance	:	m-/p-cresol 60%/40% mixture; other TS: purity >97%
Remark	:	This endpoint had been studied by other investigators and results are similar to the study mentioned above.
Reliability	:	(1) valid without restriction

Type	:	Mouse lymphoma assay
System of testing	:	L5178Y mouse lymphoma cells
Metabolic activation	:	with and without
Result	:	Positive with, weakly positive without
Method	:	other: similar to OECD Guideline 476
Year	:	1980
GLP	:	Yes

Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

Reliability : (1) valid without restriction

(2)

Type : Sister chromatid exchange assay
System of testing : Chinese hamster ovary cells

Metabolic activation : With and without
Result : Positive with and without
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

(2)

Type : Cell transformation
System of testing : Mouse BALB/C 3T3 cells

Metabolic activation : With
Result : Positive
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

(2)

Type : Unscheduled DNA Synthesis
System of testing : Rat hepatocytes

Result : Positive
Method : Other
Year : 1980
GLP : Yes
Test substance : 1:1:1 mixture of o-, m-, p-cresol iosmers

(3)

GENETIC TOXICITY "IN VIVO"

Type : Micronuclei in peripheral blood erythrocytes
Species : Mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : Oral feed
Exposure period : Daily for 13 weeks
Doses : 0, 625, 1250, 2500, 5000, 10000 ppm
Result : Negative
Method : MacGregor et al, 1983; 10000 normochromic erythrocytes were scored for each animal
Year : 1990
GLP : Yes
Test substance : m/p-cresol, 60%-40% mix TS: purity > 98%

Reliability : (1) valid without restriction

(1)

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