Chemical Name: Ethylphenols Category
Submitter: Merisol

The following chemicals are included in the category:

CHEMICAL NAME	CASRN
o-ethylphenol	90-00-6
p-ethylphenol	123-07-9
m-ethylphenol	620-17-7

As the Agency received data from High Production Challenge Program participants, it posted notice of and links to those data here for public review and comment. Companies and consortia were requested to defer any proposed new testing on their chemicals for a period of 120 days from when their Test Plans and Robust Summaries were posted to the Internet, in order to allow for technical public comment regarding the possible provision of additional existing data or other technical information which might address or eliminate the need for some new testing.

Some sponsors of chemicals submitted revised test plans and robust summaries to the Agency and referred to them as "final" submissions. EPA previously referred to the most recent submission as "revised" and has made no distinction or judgment whether a submission is final. Lastly, technical public comments on test plans and robust summaries were also provided for several chemicals/categories.

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The pdf contains the following documents:

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.

<<99LT006_.doc>> <<julyEPcategoryjustification and test plan.doc>>

Barbara Christianson
Legal Secretary
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 - 99LT006_.doc

 - julyEPcategoryjustification and test plan.doc

MERISOL USA LLC
1914 Haden Road
Houston, Texas 770015
(713) 428-5400 Fax (713) 455-0276

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]

---

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

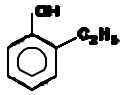
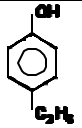
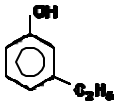
Ethylphenols

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.

AR201-13885B

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

(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	:	
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

REFERENCES

(1) NTP. 1992. Toxicity studies of cresols (CAS Nos 95-48-7, 108-39-4, 106-44-5) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program.

(2) Microbiological Associates. 1988. Subchronic toxicity of ortho-cresol in Sprague-Dawley rats. Unpublished data submitted by Microbiological Associates to US EPA.

(3) Haworth S. et al., Salmonella mutagenicity test results for 250 chemicals, Environ. Mutagen. Suppl. 1: 3-142, 1983

(4) Hazleton Laboratories America, Inc. HLC study no: 10003-0-437. Mutagenicity Test on ortho-Cresol In an In Vitro Cytogenetic Assay measuring chromosomal aberration frequencies in Chinese Hamster Ovary (CHO) Cells. June 28, 1988. Unpublished data submitted to EPA/OTS.

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(6) Hazleton Labs. Mutagenicity tests of o-cresol in a mouse lymphoma mutation assay. Unpublished data submitted to EPA/OTS (Fiche No. OTS0517693), 1988.

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(10) MRI Project No. 4822-2, March, 1980. Unpublished report.

(11) LBI Project No. 20991, July, 1981, Unpublished report.

(12) Hazelton Laboratories America Inc., James L. Ivett., Dominant Lethal Assay in Mice; para-cresol., June 30, 1989.

(13) Hazleton Labortories America, Inc., Russell C. Seranau., Mutagenicity test on ortho-cresol Drosophila Melanogaster sex-linked recessive lethal test, February 22, 1989.

(14) BRRC. 1989. Teresa L. Neeper-Bradley and Rochelle W. Tyl., Two-generation reproduction study of o-cresol (CAS No. 95-48-7) administered by gavage to Sprague-Dawley (CD) rats. December 19, 1989. Unpublished data submitted by Bushy Run Research Center to The American Chemistry Council Cresols Panel, Washington, DC.

(15) BRRC. 1988. Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to Sprague-Dawley (CD) rats. Unpublished data submitted by Bushy Run Research Center to EPA/OTS (Fiche No. OTS0517695).

(16) BRRC. 1988. Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to New Zealand White Rabbits. Unpublished data submitted by Bushy Run Research Center to EPA/OTS (Fiche No. OTS0517695).

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)

REFERENCES

(1) NTP. 1992. Toxicity studies of cresols (CAS Nos 95-48-7, 108-39-4, 106-44-5) in F344/N rats and B6C3F1 mice (feed studies). Research Triangle Park, NC, U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, National Toxicology Program.

(2) Litton Bionetics Unpublished report. Sister Chromatid Exchange Assay, Ames Test, Mouse Lymphoma Forward Mutation Assay, and Transformation Assay for a Sample Containg 33-1/3% each ortho-, meta- and para-cresol. EPA/OTS Report OTSO517528.

(3) Litton Bionetics Unpublished report. Unscheduled DNA Synthesis Assay for a Sample Containg 33-1/3% each ortho-, meta- and para-cresol. EPA/OTS Report OTSO517530.

AR201-14117

Chad Sandusky <csandusky@pcrm.org> on 12/16/2002 02:34:51 PM

Please respond to csandusky@pcrm.org

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cc:

Subject: Comments on Test Plan for Ethylphenols Category

Please find attached (in PDF format) the comments by the animal protection community on the above referenced test plan (ethylphenols category submitted by Merisol USA LLC).

Sincerely,

Chad B. Sandusky, Ph.D.
Senior Toxicologist
Physicians Committee for Responsible Medicine

HPV comments-ethylphenols-12-16.pdf

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December 16, 2002

Christine Todd Whitman, Administrator
U.S. Environmental Protection Agency
Ariel Rios Building
Room 3000, #1101-A
1200 Pennsylvania Ave., N.W.
Washington, DC 20460

Subject: Comments on the HPV Test Plan for the Ethylphenols Category

Dear Administrator Whitman:

The following comments on the Merisol USA LLC High Production Volume (HPV) Challenge test plan for the chemical class known as ethylphenol isomers are submitted on behalf of the Physicians Committee for Responsible Medicine, People for the Ethical Treatment of Animals, the Humane Society of the United States, the Doris Day Animal League, and Earth Island Institute. These health, animal protection, and environmental organizations have a combined membership of more than ten million Americans.

Merisol submitted its test plan on July 29, 2002. The ethylphenols category is comprised of three ethylphenol isomers, as follows:

Chemical	CAS Number
o-ethylphenol	9006
p-ethylphenol	123079
m-ethylphenol	620177

Merisol states in its test plan that, since the ethylphenols are generally moved into commerce as starting materials for further chemical processing, there is little consumer exposure. However, due to the large production volume of these chemicals, they are subject to the HPV program. Most are sold by Merisol as blends and not as isolated isomers.

Overall, the test plan for mixed ethylphenols proposes limits on the amount of new animal testing by grouping the various isomers of ethylphenols into one testing category. While we agree with this approach, which results in fewer animals being used in the SIDS battery, we remain concerned about the proposed testing, which includes the following:

1. Acute oral toxicity study (OECD No. 425),
2. Combined repeat dose/reproductive/developmental study (OECD No. 422) and
3. Mammalian erythrocyte micronucleus test (OECD No. 474).

All of these tests are unnecessary. If this test plan is conducted in its present form, approximately 810 animals will be killed. In addition, an acute fish toxicity study (OECD No. 203) is proposed which is also unwarranted. This study would require an additional 40 animals. Our objections are summarized later in these comments.

Merisol bases the chemical category of the ethylphenols on their chemical similarity, i.e., they are all phenols substituted with one ethyl group in one of the three positions on the phenolic ring (i.e., ortho, meta, and para positions), sharing the same molecular weight, or, in the case of the mixture, average molecular weight, and the physical-chemical properties of the isomers are similar. In addition, as stated in the Merisol test plan, methyl phenols, known as cresols, "have demonstrated that the methyl phenol isomers are remarkably equivalent in toxicity and that binary and tertitiary mixtures of cresol isomers do not produce toxic interactions among the isomers, i.e., mixtures of cresol isomers do not exhibit more than additive toxicity." In addition, the data on the cresols demonstrated "that there was no one predominately toxic isomer and that target organ for toxicity and toxic dose levels were relatively consistent across the isomers." A similar pattern would be expected for the ethyl phenols based on structural similarity among this group of isomers. Again, we agree with this assessment.

However, on page 6 of the Merisol test plan, the company states that the "details for the toxicological work on ethylphenols are unavailable....[and] no ***existing studies*** will be relied upon for HPV evaluations. Accordingly, Merisol proposed 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 but instead will develop data for each SIDS Screening Endpoint using the ethylphenol isomer mixture.... Merisol is defining ethylphenols [to be tested] as a mixture containing equal portions of o-, p- and m-ethylphenol." (emphasis added).

We strenuously object to this approach, with its inexplicable and indefensible disregard of existing data, as it will result in the needless testing and suffering of animals and violates principles of thoughtful toxicology and good science. Our objections are summarized below:

1. Merisol does not follow some of the main tenets laid out in the *Federal Register* notice in December 2000 regarding the development of test plans. It is not appropriate to create a testing category, reject the use of toxicity data on individual components in that same category, and then conduct new animal tests on an arbitrary mixture of the individual components. Apparently there are data available on the individual isomers, as Merisol states on page 6 "...that no ***existing studies*** will be used to supply data for SIDS endpoints in the Ethylphenols Category" (emphasis added). The test plan appears to deliberately ignore information available to Merisol on the individual isomers of ethylphenol that can reduce the use of animals in SIDS tests. The EPA has clearly stated that

all available data should be carefully considered before new animal tests are conducted. By choosing to ignore available data and not summarizing these data in its test plan, Merisol has violated this basic principle. We request in the strongest terms that any data available to Merisol on the isomers be summarized and its use maximized to reduce the amount of new animal tests on the mixture. In addition, any new data (from new animal tests) should be relevant in terms of hazard assessment and not duplicative of any ***existing data*** on the individual isomers. This is also a stated goal in the Federal Register, but this cannot be determined if existing data have been ignored and not included in the test plan (emphasis added). Perhaps Merisol is unaware of the guidance the EPA has provided to manufacturers in the development of test plans and the goals of minimizing the use of animals in the HPV program.

2. We have identified other data which have not been included in the evaluation of the ethylphenols and may be useful in determining data gaps. As noted above, an evaluation of all relevant information is required in the December 2000 *Federal Register*. The citations for this information are provided below, specifically:

   Initial Submission: Toxicity Report: M-Ethylphenol With Cover Letter Dated 09/28/92 (1992; EPA/OTS; Doc. #88-920009161).

   Initial Submission: Acute and Irritation Studies With 4-Ethylphenol in Rats and Rabbits With Cover Letter (1992; EPA/OTS; Doc. #88-920004538).

   Ambient Working Water Quality Guidelines for Phenols: Technical Report (April 19, 2002; prepared by the Water, Air and Climate Branch, Ministry of Water, Land and Air Protection, British Columbia, Canada) (Contains LC_{50}'s for 4-ethylphenol in fathead minnow plus extensive analysis of aquatic toxicity of various phenols in many different test systems). (http://wlapwww.gov.bc.ca/wat/wq/Bcguidelines/phenol/phenol.html)

   Safety data for o-ethylphenol (an MSDS showing two LD_{50}'s in mice of 600 mg/kg [oral] and 172 mg/kg [intraperitoneal]) (http://www.physchem.ox.ac.uk/MSDS/ET/o-ethylphenol.html)

   MSDS (Aldrich Chemical Company, valid through 1/2002, showing an interperitonel LD_{50} in mice of 138 mg/kg) (http://www.conncoll.edu/offices/envhealth/MSDS/chsmistry/E/4-Ethylphenol,-99.html).

   Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals (1992; Zeiger et al.; Environmental Molecular Mutagen, 19 Suppl21:2-141).

A thorough evaluation of all of the toxicity data as a whole would likely obviate the need for additional animal testing under the HPV program. We strongly request that Merisol access this information and revise its testing plan accordingly. This will assist in further reducing the unnecessary suffering of animals used in these tests.

3. A new LD_{50} test on the mixture, when there is apparently an individual oral LD_{50} reported (600 mg/kg in mice; see number 2 above) for the o-ethylphenol isomer, is absolutely unwarranted. Furthermore, there are two EPA reports cited above that also apparently contain acute toxicity data on m- and 4-ethylphenol, respectively. These should be assessed prior to proposing any new lethal dose testing. Any new information gathered from this test will not enhance the understanding of the acute oral toxicity of the mixture nor is acute toxicity needed for the individual isomers, as apparently at least one of the three has been tested (and this is sufficient for the category as a whole using the "bridging-of-data" approach). Merisol has stated in its own test plan that mixtures of cresols do not produce toxic interactions among the isomers and a similar pattern would be expected for the mixture of ethylphenols (we agree with this conclusion). In summary, acute oral toxicity testing is completely unwarranted and a violation of the HPV program principles. If for some reason, Merisol insists on conducting an acute oral toxicity test for the mixture of ethylphenols mixture, we urge the company to use the *in-vitro* cytotoxicity assays. This approach was incorporated into the HPV program as a result of the National Toxicology Program- and National Institute of Environmental Health Sciences-sponsored *Workshop on International on* In-Vitro *Methods,* held on October 17-20, 2000. This workshop reviewed the validation status of available *in-vitro* methods for predicting acute oral toxicity (among other goals). As a result of this workshop, the EPA encouraged those participating in the HPV program to "consider using the recommended *in-vitro* tests...as a supplemental component in conducting any new *in-vivo* acute oral toxicity studies...[and] to note the intention to use these protocols in the HPV Challenge test plans submitted to EPA." The two *in-vitro* tests recommended are the neutral red uptake assays using the mouse fibroblast cell line BALB/c 3T3 and normal human keratinocytes. Guidance on these recommended *in-vitro* tests, protocols for their use and a reporting template for results can be found on the ICCVAM Web site at *http://iccvam.niehs.nih.gov/docs/docs.htm#invitro*. Finally, although Merisol states that it "may" use alternative testing strategies, it should be noted that its proposal to use the traditional LD_{50} is unacceptable under any circumstances as TG 401 is being deleted internationally.

4. Merisol proposes conducting an Ames *in-vitro* bacterial mutation assay (OECD No. 417), as well as a mammalian *in-vivo* erythrocyte micronucleus test (OECD No. 474). The latter test should be deleted. If the results of the Ames assay are negative, no additional *in-vivo* testing should be conducted, especially in a screening level program. The December 2000 *Federal Register* notice states that

genotoxicity testing should be conducted *in vitro* unless physical properties preclude use of such studies.

5. The same principle apples to fish toxicity, as there is an extensive Canadian report on the aquatic toxicity of the phenols, including fathead minnow LC_{50} data for 4-ethylphenol (see number 2 above). Additional studies in fish are not warranted, as the above report is an official Canadian document, the contents of which should meet the HPV SIDS requirement.

6. Finally, there is not a data vacuum surrounding isomers of ethylphenols' reproductive and developmental toxicity. A developmental toxicity study under Good Laboratory Practice's has been conducted on 2,6-xylenol as well as extensive testing on cresols, the toxicity database of which was used in part to justify the mixed ethylphenols category. The cresols are methylphenols and 2,6-xylenolol is a di-methyl phenol instead of being ethylphenols, which are the subject of this test plan. Thus, with everything that is known about the mixed xylenols category and cresols category, further testing of the ethylphenols for reproductive/developmental toxicity is unlikely to provide any new insight into this toxicity for this endpoint. Rather, an *in-vivo* study using 750 animals in stressful experiments is neither warranted nor justified. As an alternative to *in-vivo* testing, an *in-vitro* embryotoxicity test would be adequate to characterize any possible adverse reproductive effects of these materials. If, in fact, Merisol insists on further exploration of developmental endpoints, we urge it to consider the use of an *in-vitro* test for embryotoxicity (a critical endpoint in developmental toxicity) using the rodent Embryonic Stem Cell Test (EST) protocol that has been validated by the European Centre for the Validation of Alternative Methods (ECVAM). For additional information, please refer to E. Genschow et. al., "The ECVAM international validation study on *in-vitro* embryotoxicity tests: results of the definitive phase and evaluation of prediction models" (*Alternatives to Laboratory Animals* 30:151-76, 2002). If a positive result is found, the substance should be treated as a developmental toxicant/teratogen, and no further testing should be conducted under the screening-level HPV program.

7. Although some of the data identified in objection 2 above may have been generated by other companies, we strongly encourage Merisol to coordinate any new SIDS work with others who may have already conducted duplicative testing in animals. This approach is consistent with the EPA's stated goals of maximizing the use of existing data in order to limit additional animal testing. We have encouraged the EPA in past test plan comments to ensure inter-industry cooperation in the development of chemical categories and test plans, including comments on the American Petroleum Institute Petroleum Coke test plan, the Phosphite Producers HPV Consortium test plan on tris(nonylphenol)phosphite, and the General Electric test plan on p-cumylphenol. We are concerned that the EPA is not adequately encouraging inter-company and inter-industry cooperation in the development of test plans and chemical categories, thus greatly increasing the number of animals killed in the HPV program.

Summary:

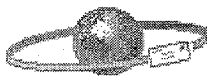
Merisol has inappropriately stated that existing data available on the individual isomers of the ethylphenols will not be used to evaluate data gaps for the HPV SIDS battery. Rather, it has ignored these data, as well as other data cited in these comments, and proposed a complete SIDS battery on the mixture of these three isomers. There may be sufficient data on the individual ethylphenol isomers (which have not been included in Merisol's assessment), in conjunction with what is known from testing on methylphenols (cresols category) and di-methylphenols (mixed xylenols category), with regards to mixture interactions (or lack thereof), which would render any new animal tests with ethylphenols completely unnecessary. In spite of this fact, Merisol has proposed tests on animals and has failed to fully utilize the available toxicity data on ethylphenols to meet HPV SIDS requirements. Furthermore, conducting these new tests clearly violates Sections 1 and 8 of the animal protection agreement and the EPA's December 2000 *Federal Register* notice that states a) "In analyzing the adequacy of data, participants shall conduct a thoughtful, qualitative analysis rather than use a rote checklist approach. Participants may conclude that there are sufficient data, given the totality of what is known about a chemical, including human experience, that certain endpoints need not be tested" and b) "As with all chemicals, before generating new information, participants should further consider whether any additional information obtained would be useful or relevant." Conducting a new LD_{50} study and a new repeat dose/reproductive/developmental screening study on the mixture of ethylphenols without a full evaluation of the existing data available on the individual isomers violates the standard set forth in the *Federal Register* as well as good science and thoughtful toxicology.

I look forward to a prompt and favorable response to our concerns. I may be reached at 202-686-2210, ext. 302, or via email at *csandusky@pcrm.org*.

Sincerely,

Chad B. Sandusky, Ph.D.
Senior Toxicologist

AR201-14119



Karen_Florini@environmentaldefense.org on 12/17/2002 06:29:55 PM

To: oppt.ncic@epamail.epa.gov, ChemRTK HPV@EPA, Rtk Chem/DC/USEPA/US@EPA, Karen Boswell/DC/USEPA/US@EPA, bchristianson@lawbc.com
cc: lucierg@msn.com, rdenison@environmentaldefense.org, kflorini@environmentaldefense.org

Subject: Environmental Defense comments on the Ethylphenols Category (ethylphenol isomers)

(Submitted via Internet 12/17/02 to oppt.ncic@epa.gov, hpv.chemrtk@epa.gov, boswell.karen@epa.gov, chem.rtk@epa.gov, lucierg@msn.com and bchristianson@lawbc.com)

Environmental Defense appreciates this opportunity to submit comments on the robust summary/test plan for ethylphenol isomers.

The test plan for ethylphenol isomers was prepared by Merisol USA LLC. This plan is very similar to a companion plan on xylenol isomers submitted by Merisol on the same date. There are three isomers included in this plan, namely o-ethylphenol, m-ethylphenol, and p-ethylphenol. They are used as intermediates in the manufacture of a wide variety of products such as resins, flame retardants, antioxidants and insulating varnishes.

Surprisingly, there are no data available on the ethylphenols deemed reliable for use by the HPV Challenge Program. Accordingly, the sponsor proposes a complete spectrum of studies to provide data on chemistry, environmental fate, health effects and ecotoxicity. The proposed studies would be conducted on a mixture containing equal amounts of all three isomers. The sponsor contends that all of the isomers should possess the same toxicological and environmental fate properties based on available data for the corresponding methylphenol isomers (cresols) including a very thorough set of studies conducted by the NTP. In these studies, the cresols demonstrated a low order of toxicity but some genetic toxicity assays (i.e. cell transformation) were positive. The cresols, like the ethylphenols, contain a free hydroxyl group that renders these molecules readily biodegradable.

We agree with the sponsor's proposal to conduct a full spectrum of HPV studies on a mixture of ethylphenol isomers. However, we recommend that cytotoxicity studies be used instead of acute toxicity tests in rodents. Inasmuch as these substances likely possess low acute toxicity and high-dose data will be obtained from the range-finding component of the repeat dose study, conducting separate acute toxicity tests in rodents is an unnecessary use of animals.

Although the sponsor's contention that the ethylphenols and cresols possess similar toxicological and environmental properties is probably true, we do have some concerns that once the data come in this contention could be contradicted by indications that the ethylphenols should not be handled as a category (i.e., if the initial round of data indicate that the category is not "well behaved"). While such an outcome would be somewhat surprising, the current near-total absence of data on these ethylphenols means that it cannot be ruled out. Thus, after data are generated under this test plan, they should be reviewed to determine if in fact the category performs as anticipated; if it does not, generation of additional data for the HPV endpoints for the individual members of the category will be needed (members of the public should be given the opportunity to comment on this).

In the meantime, we recommend that the sponsor conduct molecular studies to help verify that the three isomers belong in the same category. In

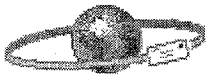
particular, we recommend that the sponsor conduct gene-expression studies in in vitro systems using microarray technologies to determine if all the isomers produce the same pattern of gene-expression changes. These data are not required by the HPV program but they would, in conjunction with the studies already proposed by the sponsor, provide a solid database to indicate whether or not the ethylphenols category is scientifically justified.

Thank you for this opportunity to comment.

George Lucier, Ph.D.
Consulting Toxicologist, Environmental Defense

Karen Florini
Senior Attorney, Environmental Defense

201-14156



Cox SMTP west <beverlyjm@cox.net> on 12/19/2002 03:22:31 PM

To: oppt.ncic@epamail.epa.gov, ChemRTK HPV@EPA, Rtk Chem/DC/USEPA/US@EPA, Karen Boswell/DC/USEPA/US@EPA, bchristianson@lawbc.com

cc:

Subject: Comments

PETA reports that,"Merisol apparently has access to existing data but is choosing to ignore them, preferring instead to run painful new LD50 reproductive, developmental, and genetic tests on animals". The appropriate name for these tests should be "Frankenscience" which is an attempt at using science for unscientific, cruel, unethical tests that generate fear, prolonged agony, and death for the animal victims.
Beverly MacKenzie
San Juan Capistano, CA

201-14166

To: oppt.ncic@epamail.epa.gov, hpv.chemrtk@epamail.epa.gov, Rtk Chem/DC/USEPA/US@EPA, Karen Boswell/DC/USEPA/US@EPA, bchristianson@lawbc.com
cc: NAmerica-sales@merisol.com

Subject: Merisol USA to kill 1,700 animals in cruel, pointless tests

Chemical company **Merisol USA** has submitted two testing plans to the U.S. Environmental Protection Agency (EPA) that will kill more than 1,700 animals in obviously cruel and pointless tests. Your company's proposals blatantly violate the most minimal animal-welfare provisions of the EPA's high production volume (HPV) chemical-testing program. We are not fooled by this company's submission of these plans through a law firm in an apparent attempt to keep its identity and contact formation away from public scrutiny.

PETA explains the plans as follows:

- Merisol already has LD50 (lethal dose poisoning) test data on five of the six xylenol chemicals that it manufactures. Yet, instead of using those data, the company is planning to kill more animals in another LD50 test of an arbitrary and meaningless mixture of these six chemicals.
- In its test plan for ethylphenols, Merisol states up front that "no existing studies will be relied upon for HPV evaluations." In other words, Merisol apparently has access to existing data but is choosing to ignore them, preferring instead to run painful new LD50, reproductive, developmental, and genetic toxicity tests on animals.

The HPV program guidelines call for companies to use existing data wherever possible instead of conducting new tests. I urge that **these test plans are denied.**

This is ill-conceived and ill-planned. Do not let the EPA become an accessory to this planned crime.

Sincerely,
--
Michael Baraz
331 Shady Lane
Elmhurst, IL 60126

2002 DEC 27 PM 12:13

December 20, 2002

Kenneth P. Morgan
Manager, Technical Support Services
Merisol USA LLC
1914 Haden Road
Houston, Texas 77015-6498

Dear Mr. Morgan:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Ethylphenols Category posted on the ChemRTK HPV Challenge Program Web site on August 16, 2002. I commend the Merisol USA LLC for its commitment to the HPV Challenge Program.

EPA also must bring to your attention the fact that the acute toxicity test which you have proposed is specifically not recommended for use in the HPV Challenge Program (65 FR 81695) where the recommended guideline is OECD TG 425 (the "Up and Down Method"). In addition, the Organization for Economic Cooperation and Development (OECD) has made the decision to remove OECD TG 401, and test data using the guideline generated after December 20, 2002 need not be accepted by other OECD countries under Mutual Acceptance of Data. Note, also, that EPA encourages Challenge sponsors that have proposed acute toxicity testing to use an in vitro dose range-finding protocol to set the starting dose for the Up and Down test. Information on this protocol is available at http://www.epa.gov/chemrtk/toxprtcl.htm. Finally, EPA recommends an in vitro chromosomal aberration study instead of the in vivo micronucleus (OECD 474) proposed.

With the successful completion of the testing needed to address the category proposal, EPA will consider this as meeting a sponsorship commitment.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that Merisol advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
W. Penberthy
A. Abramson
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Ethylphenols Category

SUMMARY OF EPA COMMENTS

The sponsor, Merisol USA LLC, submitted a test plan and robust summaries to EPA for the mixed ethylphenols category dated July 29, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on August 16, 2002. The category consists of 2-ethylphenol (o-ethylphenol, CAS No. 90-00-6); 3-ethylphenol (m-ethylphenol, CAS No. 620-17-7); and 4-ethylphenol (p-ethylphenol, CAS No. 123-07-9).

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. Given the close structural similarity of these isomers, the similar physicochemical properties, and the evidence demonstrating similar toxicities of members of an analogous series of methylphenol (cresol) isomers, it is reasonable to expect that the ethylphenol isomers will have toxicities similar to each other.

2. Physicochemical Properties and Environmental Fate. The submitted physicochemical data on three individual isomers are adequate for the purposes of the HPV Challenge Program. EPA believes that hydrolysis testing is not necessary. All new and existing data need to be presented in robust summary format.

3. Health Effects. EPA agrees with the submitter's test plan for addressing all health effects endpoints using the ethylphenol mixture but recommends testing a commercial ethylphenols mixture that either (a) is sold in the highest production volume, or (b) has the highest percentage of ethylphenol isomers.

4. Ecological Effects. EPA agrees with the submitter's test plan for addressing the ecological effects endpoints using the equimolar mixture. EPA notes that there is a published fish study for 4-ethylphenol (Geiger, 1986) not cited in the Test Plan, and in addition existing xylenols data could be used as supporting data for ethylphenols.

EPA requests that the submitter advise the Agency within 90 days of any modifications to this submission.

EPA COMMENTS ON THE ETHYLPHENOLS CHALLENGE SUBMISSION

General

This submission is similar to the Xylenols Category submission from the same sponsor. In reviewing both submissions, it appears that most of the submitter's commercial products are mixtures of xylenols, phenols, cresols, and ethylphenols. According to the Merisol Web site (www.merisol.com), the following xylenol products are available for sale: 2,4/2,5 xylenol mixture; "mixed xylenols and ethylphenols"; high purity xylenols (pure 3,4-isomer listed as what is currently available); and "blended cresylic acid products" (what appears to be the starting Merisol fraction used to develop the cresols, xylenols, and ethylphenols).

Table 1 in the test plan states that only 57.1% of the Merisol products contain all three ethylphenol isomers, but provides no information on the percentage composition range for xylenols, phenols, cresols, and ethylphenols in those products. The submitter needs to provide specific information on the percentages of the ethylphenol isomers in typical commercial products, with a description of the rest of the product composition.

Category Definition

The submitter has proposed a category of mixtures of three ethylphenol isomers: 2-ethylphenol; 3-ethylphenol; and 4-ethylphenol. Binary mixtures of the ethylphenol isomers constitute 42.3% of the blends and ternary mixtures compose 57.1% of the blends. The definition lacks specific information on composition (see previous section).

Category Justification

EPA agrees with the submitter's category justification. The justification is based on the close structural relationship of the ethylphenol isomers, and their similar physicochemical, and anticipated similar environmental and toxicological properties. The submitter has provided data on an analogous series of cresol isomers, which according to the submitter, demonstrate their close structural similarity, their similar physicochemical properties, and their similar toxicities. The submitter further states that it is reasonable to expect that the ethylphenol isomers will also have toxicities similar to each other. The submitter states that the toxicological properties of the ethylphenol mixtures will not significantly vary with the proportion of the ethylphenol isomers in the mixtures. However, for health effects, EPA prefers that the commercial substance be tested rather than a equimolar mixture.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, partition coefficient and water solubility).

The submitted physicochemical data on three individual isomers are adequate for the purposes of the HPV Challenge Program.

The submitter needs to check the melting point values for p-ethylphenol and m-ethylphenol reported in Table 3 of the test plan. EPA found in EPIWIN and the CRC manual melting point values of 45 and 47 °C for p-ethylphenol (the submitter reported -4 °C), and -4 °C for m-ethylphenol (the submitter reported 46 °C).

Environmental Fate (photodegradation, biodegradation, fugacity, stability in water).

EPA agrees with the submitter's test plan for addressing environmental fate endpoints using the equimolar mixture. However, EPA believes that hydrolysis testing is not appropriate for these substances.

Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity).

The submitter acknowledged that available ethylphenol data may not be reliable and will not be used for the purposes of the HPV Challenge Program. Because ethylphenols exist predominantly as mixtures in commerce, the submitter has proposed testing an equimolar mixture of the three ethylphenols to assess the potential hazards of exposure to ethylphenol-containing substances. The results of this testing would be applicable to all mixtures of ethylphenols and to each of the three individual isomers. Testing would include acute mammalian toxicity, a combined repeated-dose/reproductive/developmental toxicity screen, and genetic toxicity (assays for bacterial mutagenicity and mammalian erythrocyte micronuclei) and would be done according to OECD guidelines. EPA recommends that the submitter consider testing a commercial ethylphenols mixture that either (a) is sold in the highest production volume, or (b) has the highest percentage of ethylphenol isomers.

In Attachment I, a table titled “Cresols Isomer Mammalian Toxicity Comparison,” it is difficult to compare the reproductive and developmental toxicity data for the three separate cresol isomers because presented dose levels were not clearly identified as NOAELs, no LOAELS were reported, and identified adverse effects were not associated with specific dose levels. Furthermore, robust summaries were not submitted for the two-generation reproductive toxicity study of m-cresol. More clearly identified NOAELs and LOAELS (with associated effects) would enhance the interpretation of the results presented in this table. A similarly-designed table should be prepared for acute and repeated-dose oral toxicity as well.

Ecological Effects (fish, invertebrates, and algae).

EPA agrees with the submitter’s test plan for addressing all ecological effects endpoints using the equimolar mixture.

Specific Comments on the Robust Summaries

None.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modification to its submission.

References

Geiger, D.L., Poirier, S.H., Brooke, L.T., and Call, D.J. 1986. “Acute Toxicities of Organic Chemicals to Fathead Minnows (*Pimephales Promelas*)” Volume III, Center for Lake Superior Environmental Studies, University of Wisconsin-Superior, US Environmental Protection Agency Cooperative Agreements, Superior, Wisconsin, USA.

201-14457

NCICHPV
Sent by: Mary-Beth Weaver

05/13/2003 09:02 AM

To: NCIC HPV, moran.matthew@epa.gov
cc:
cc:
Subject: Merisol -- Ethylphenols Category

Barbara Christianson <BChristianson@lawbc.com> on 05/12/2003 04:51:59 PM

To: Christine Whitman/DC/USEPA/US@EPA
cc: Richard Hefter/DC/USEPA/US@EPA, "Kenneth P. Morgan "<ken.morgan@merisol.com>, "'oppt.ncic@epa.gov'" <oppt.ncic@epamail.epa.gov>, Rtk Chem/DC/USEPA/US@EPA, "Lisa M. Campbell" <LCAMPBELL@lawbc.com>

Subject: Merisol -- Ethylphenols Category

Appended is Merisol's proposed category and test plan for the Ethylphenols Category as part of its commitment under EPA's HPV Challenge Program. Please let us know if you have any questions.

<<99LT008_.doc>> <<RevisedEPMay_.doc>>

Barbara Christianson

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201-14457

MERISOL USA LLC
1914 Haden Road
Houston, Texas 770015
(713) 428-5400 ▯ Fax (713) 455-0276

May 12, 2003

Via E-Mail and Regular Mail

The Honorable 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:

On July 29, 2002, Merisol USA LLC (Merisol) submitted its proposed category approach and test plan for the Ethylphenols Category as part of its commitment under EPA's High Production Volume (HPV) Challenge Program. 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-l 7-7)

Merisol received comments from EPA in a letter, dated December 20, 2002. Appended are the Ethylphenols test plan and robust summaries, which have been revised to incorporate the comments from EPA. The major changes that have been made to the appended document include:

- **Test Substance:** At EPA's request, Merisol has modified the test mixture to more closely resemble a Merisol product. The revised test plan indicates our intent to test a mixture containing portions of ethylphenol isomers normalized to match the ratios of ethylphenol isomers occurring in an actual commercial product containing the highest percentage of all three ethyphenols.

- **Robust Summaries:** Merisol has prepared additional robust summaries which are appended to the test plan.

- **Cresols:** The revised test plan includes a further explanation for Merisol's discussion of the cresols data to ensure it is clear that we are not relying on

- **Cresols:** The revised test plan includes a further explanation for Merisol's discussion of the cresols data to ensure it is clear that we are not relying on the cresols data for conclusions about ethylphenols with regard to HPV testing requirements.

- **Testing Proposal:** Merisol has modified its testing proposal, as recommended by EPA, with regard to physicochemical properties, biodegradation, photodegradation, hydrolysis, fugacity, ecological effects, and acute and genetic toxicity testing.

- **Environmental Toxicity and Fate:** Merisol has added an environmental toxicity and fate section to discuss environmental toxicity, biodegradation, and photolysis.

- **Corrections:** Merisol has corrected values for boiling points, melting points, octanol/water partition coefficient, and vapor pressure.

As discussed previously with EPA, Merisol intends to conduct the ethylphenols testing following its testing program for its mixed xylenols category, so that the testing results from mixed xylenols can inform Merisol as to its proposed testing program for the ethylphenols. Testing for the mixed xylenols likely will be completed in 2005; testing for ethylphenols then would begin at that time.

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)

REVISED

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

CATEGORY JUSTIFICATION AND TEST PLAN

ETHYLPHENOL ISOMERS

Submitted by:
MERISOL USA LLC
Houston, Texas

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May 12, 2003

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 204.5°C, 218.0°C and 218.4°C, 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

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. The Merisol product containing all three ethylphenol isomers that is sold in the greatest volume and that contains the highest percentage of ethylphenol isomers is WES 297. This product contains 18.5% ethylphenols, the highest percentage in any Merisol product containing 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 portions of ehthylphenol isomers normalized to match the ratios of ethylphenol isomers occuring in an actual commercial product containing the highest percentage of all three ethyphenols. The composition of the proposed Mixed Ethylphenol Test Mixture is:

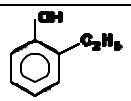
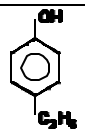
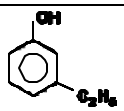
Ethylphenol Isomer	Mole % in Test Mixture
o-ethylphenol (CAS # 90006)	25.9
p-ethylphenol (CAS# 123079)	33.0

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.

m-ethylphenol (CAS# 620177). 41.1.

This mixture mimics worker and consumer exposure to a commercial product but allows for the study of ethylphenol isomers without confounding effects of non-ethylphenol product components. It 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 2.68 to 2.77 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 0.05 to 0.16 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 another 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 likewise 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	204.5ºC	218.0ºC	218.4ºC
Melting Point	-3.3ºC	45.1ºC	-4ºC
Octanol/Water Partition Coefficient	2.72	2.68	2.77
Water Solubilty	5340 mg/L @ 25ºC	4900 mg/L @ 25ºC	Slightly soluble
Vapor Pressure	0.16 mmHg@ 25ºC	0.07 mmHg@ 25ºC	0.05 mmHg@ 25ºC
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] We describe the cresols data below because we believe that the ethylphenol isomers

[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

will act analogously based on their similar chemical/physical properties; we do not believe, however, that the data support otherwise relying on the cresols data for conclusions about mixed ethylphenols with regard to HPV testing requirements, and we do not present these data for that purpose.

Attachment 1 to this document presents in tabular form summaries of developmental 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.

Environmental Toxicity and Environmental Fate

The acute aquatic environmental toxicity of the p-ethyphenol has been characterized in a freshwater fish species. The EC50 value from this study was 10.4 mg/L. Biodegradaton of each of the ethylphenol isomers has been investigated for aqueous anaerobic (o-ethylphenol) and aqueous aerobic degradation (meta- and para-ethylphenol). Complete degradation was not achieved in the tests, but 23-93% of the compound was degraded within 8 weeks.

There is potential for photolysis of each of the ethylphenol isomers. Atmospheric half-lives in light range from 5-9 hours. The manufacture and use pattern for ethylphenols does not afford significant opportunity for UV light exposure, so the importance of this mechanism for degradation would be limited to spills of the ethylphenols or ethylphenol-containing products.

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longer exposures in the 13-week study when compared to the effects seen with similar doses in the 28-day study."

CATEGORY TEST PLAN

Details for the toxicological work on ethylphenols are unavailable. Thus, while the existing mammalian and ecological toxicology data for methyl phenols, when viewed as a whole, strongly support toxicology data development on an ethylphenol mixture as a category for HPV testing, the data may not be relied upon for HPV evaluations.

Merisol proposes that submitted data for physiochemical properties, photodegradation, and toxicity to fish are sufficient for addressing these endpoints for the HPV Challenge Program. Merisol also proposes not to perform hydrolysis testing, which is not appropriate for these substances, and determination of fugacity endpoint, which is fulfilled by modeling and cannot be run appropriately with mixtures. Accordingly, Merisol proposes that the studies listed in Table 5 will be developed on the Ethyphenol Test Mixture (composition shown below) and data from those studies used to supply data for SIDS endpoints in the Ethylphenols Category.

Ethylphenol Isomer	Mole % in Test Mixture
o-ethylphenol (CAS # 90006)	25.9
p-ethylphenol (CAS# 123079)	33.0
m-ethylphenol (CAS# 620177).	41.1.

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.

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. ENVIRON-MENTAL FATE	
Biodegradation	OECD Test Guideline 301
2. HEALTH EFFECTS	
Acute Toxicity	Acute Oral Toxicity: OECD Health Effects Test Guideline 425
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; *In vitro* chromosomal aberration test OECD Guideline 473
3. ECOTOXICITY	
Daphnia	Acute Toxicity to Aquatic Invertebrates: OECD Test Guideline 202
Algae	Acute Toxicity to Aquatic Plants (Algae): OECD Test Guideline 201

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	NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	Maternal NOAEL = 5 mg/kg/day Maternal LOAEL = 50 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	Developmental NOAEL = 50 mg/kg/day No embryotoxicity or fetotoxicity. Skeletal variations observed in high-dose pups (100mg/kg/day)	Developmental NOAEL= 100 mg/kg/day No embryotoxicity or fetotoxicity.	Developmental NOAEL = 100 mg/kg/day No embryotoxicity or fetotoxicity.
Rat Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	Maternal NOAEL 175 mg/kg/day Maternal LOAEL = 450 mg/kg/dayHypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 16% mortality.	Maternal NOAEL = 175 mg/kg/day Maternal LOAEL = 450 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 0% mortality.	Maternal NOAEL =175 mg/kg/day Maternal LOAEL = 450mg/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	Developmental NOAEL = 175 mg/kg/day No increase in malformations, visceral variations at the high-dose.	Developmental NOAEL= 450 mg/kg/day No increase in malformations. No increase in variations.	Developmental NOAEL = 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	Parental NOEAL 30 mg/kg/day Parental LOAEL = 175 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.	Parental NOAEL <30 mg/kg/day Effects included high-dose mortality (450 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 and F1 parents.	Parental NOAEL = 30 mg/kg/day Parental LOAEL = 175 mg/kg/day. High-dose mortality (450mg/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	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in F1 or F2 pups.	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in F1 or F2 pups.	F1 and F2 NOAEL = 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.

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

PHYSICAL-CHEMICAL ELEMENTS
m-Ethylphenol (CAS 620-17-7)

Type	: Melting Point
Value	: -4.0 ^{o}C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: 1955 or earlier
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Terres, *Brennstoff Chemie*,36,272 (1955)

Type	: Boiling Point
Value	: 218.42 ^{o}C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: Unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type	: Vapor Pressure
Value	: 0.05 mmHg at 25^{o}C
Method	: Calculated from vapor pressure constants in reference
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Estimated < 5% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR values regressed from seven literature references.

Type : Partition Coefficient
Value : Log Kow = 2.77
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Water Solubility
Value : 2.3 wt % at 127.3 ^{o}C
Method : Unknown
GLP : Unknown
Year : 1955 or earlier
Remarks : Expected to be slightly soluble @ 25^{o}C
Quality : Unknown
Reliability : (2) Reliable with restrictions

(5) Terres, *Brennstoff Chemie*, 36, 272 (1955)

Type : pKa Value
Value : 10.17 @ 20^{o}C
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(6) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A19, p. 323

ENVIRONMENTAL FATE ELEMENTS
m-Ethylphenol (CAS 620-17-7)

Type : Atmospheric fate
Value : T1/2 = 5 hours
Method : Structure activated method
GLP : Unknown
Year : 1993
Remarks : Vapor-phase m-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 8.4x10S-11 cc/molecule-sec @ 25^{o}C
Quality : Unknown

Reliability : (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Aqueous aerobic degradation
Value : 93% removal in 37 days
Method : Water column passed through acclimated soil
GLP : Unknown
Year : 1989
Remarks : Laboratory study
Quality : Unknown
Reliability : (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX B
ROBUST SUMMARY FOR o-ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
o-Ethylphenol (CAS 90-00-6)

Type : Melting Point
Value : -3.3 ^{o}C
Decomposition : No
Sublimation : No
Method : Unknown
Year : 1963 or earlier
GLP : Unknown
Remarks : None
Quality : Estimated < 1% error
Reliability : (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR value taken from Biddescombe, *J. Chem. Soc.*,5764, (1963)

Type : Boiling Point
Value : 204.5 ^{o}C
Decomposition : No
Sublimation : No
Method : Unknown
Year : Unknown
GLP : Unknown
Remarks : None
Quality : Estimated < 1% error

Reliability : (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type : Vapor Pressure
Value : 0.16 mmHg at 25°C
Method : Calculated from vapor pressure constants in reference
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Estimated < 5% error
Reliability : (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR values regressed from nine literature references.

Type : Partition Coefficient
Value : Log Kow = 2.72
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : Water Solubility
Value : 5340 mg/L @ 25°C
Method : Uknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(5) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type : pKa Value
Value : 10.47 @ 20°C
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(6) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A19, p. 323

ENVIRONMENTAL FATE ELEMENTS
o-Ethylphenol (CAS 90-00-6)

Type	: Atmospheric fate
Value	: T1/2 = 9 hours
Method	: Structure estimated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase o-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 4.2 x 10E-11 cc/molecule-sec @ 25^{o}C
Quality	: Unknown
Reliability	: (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous anaerobic degradation
Value	: 23-42% removal in 8 weeks
Method	: Groundwater column inoculated into anaerobic digestor
GLP	: Unknown
Year	: 1983
Remarks	: Laboratory study
Quality	: Unknown
Reliability	: (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX C
ROBUST SUMMARY FOR p-ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOL CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
p-Ethylphenol (CAS 123-07-9)

Type	: Melting Point
Value	: 45.08^{o}C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: Unknown

GLP : Unknown
Remarks : None
Quality : Estimated < 5% error
Reliability : (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type : Boiling Point
Value : 217.99 ^{o}C
Decomposition : No
Sublimation : No
Method : Unknown
Year : Unknown
GLP : Unknown
Remarks : None
Quality : Estimated < 1% error
Reliability : (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type : Vapor Pressure
Value : 0.07 mmHg at 25^{o}C
Method : Calculated from vapor pressure constants in reference
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Estimated < 10% error
Reliability : (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR values regressed from three literature references.

TYPE : Partition Coefficient
Value : Log Kow = 2.68
Method : Unknown
GLP : Unknown
Year : Unknown
Remarks : None
Quality : Unknown
Reliability : (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Log Kow
Value	: 2.66 / 2.81
Method	: Unknown / Calculated
GLP	: Unknown / Unknown
Year	: Unknown / Unknown
Remarks	: None / None
Quality	: Unknown / Unknown
Reliability	: (2) Reliable with restrictions

(5) Verschueren, "Handbook of Environmental Data on Organic Chemicals"

Type	: Water Solubility
Value	: 4900 mg/L @ 25^{o}C
Method	: Uknown
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(6) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: pKa Value
Value	: 10.38 @ 20^{o}C
Method	: Unknown
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(7) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. A19, p. 323

ECOTOXICITY ELEMENTS
p-Ethylphenol (CAS 123-07-9)

Type	: Acute
Species	: Fathead minnow
Sex	: Not stated
Strain	: Not applicable
Route of administration	: Flow-through
Exposure period	: 96 hr
Frequency of treatment	: One day
Post exposure period	: Not applicable
Doses	: 0, 10.5, 16.1, 24.8, 38.2 and 58.9 mg/l, analytical verification
Control group	: Untreated
LC50	: 10.4 mg/l

Method	: Evaluate test water quality, fish behavior and pharmacotoxic signs, body weight and survival.
Year	: 1985
GLP	: Not stated
Test substance	: 4-ethylphenol 99% pure
Reliability	: (2) Reliable with restrictions

(8) Geiger, D. L., et al., Acute toxicities of organic chemicals to fathead minnows, Vol. III. Center for Lake Superior Environmental Studies, U. of Wisciensin – Superior. US EPA Cooperative Agreements Superior, WI., p 195, 1985.

ENVIRONMENTAL FATE ELEMENTS
p-Ethylphenol (CAS 123-07-9)

Type	: Atmospheric fate
Value	: T1/2 = 9 hours
Method	: Structure estimated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase p-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 4.2 x 10E-11 cc/molecule-sec @ 25^{o}C
Quality	: Unknown
Reliability	: (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous aerobic degradation
Value	: 76% removal in 37 days
Method	: Water column passed through acclimated soil
GLP	: Unknown
Year	: 1989
Remarks	: Laboratory study
Quality	: Unknown
Reliability	: (4) Not Assignable

(10) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX D
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 E
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 F
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

(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	:	
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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(16) BRRC. 1988. Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to New Zealand White Rabbits. Unpublished data submitted by Bushy Run Research Center to EPA/OTS (Fiche No. OTS0517695).

APPENDIX G
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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JuanB Perez/DC/USEPA/US
05/08/2006 08: 13 AM

To NCIC HPV@EPA
cc
bcc
Subject Fw: Merisol -- Ethylphenols Category

----- Forwarded by JuanB Perez/DC/USEPA/US on 05/08/2006 08:12 AM ----

"Allison J. MacDougall" <AMACDOUGALL@lawbc.com>
05/05/2006 09: 17 PM

To Stephen Johnson/DC/USEPA/US@EPA
cc Mark Townsend/DC/USEPA/US@EPA, NCIC OPPT@EPA, Rtk Chem@EPA, "Kenneth P. Morgan " <ken.morgan@merisol.com>, "Lisa M. Campbell, Esquire " <LCAMPBELL@lawbc.com>
Subject Merisol -- Ethylphenols Category

Appended is Merisol's final category and test plan for the Ethylphenols Category as part of its commitment under EPA's HPV Challenge Program. Please let us know if you have any questions.

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201-14457A

May 5, 2006

Via E-Mail and Regular Mail

The Honorable Stephen L. Johnson
Administrator
U.S. Environmental Protection Agency
P.O. Box 1473
Merrifield, VA 22 116

Re: Final HPV Challenge Program Submission for the Ethylphenols Category -- EPA Registration No. - -

Dear Administrator Johnson:

On May 12, 2003, Merisol USA LLC (Merisol) submitted its revised category approach and test plan for the Ethylphenols Category as part of its commitment under EPA's High Production Volume (HPV) Challenge Program. The Ethylphenols Category consists of the following three chemicals:

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

Appended are the final Ethylphenols Category test plan and robust summaries which incorporate the results from Merisol's testing for the Ethylphenols Category as described in its test plan and explain why the newly conducted data support the category approach initially proposed by Merisol. It is Merisol's understanding that the U.S. Environmental Protection Agency (EPA) will post this document on its website identified as a "final" submission. With the submission of the final test plan and robust summaries, Merisol has completed its commitment under the HPV Challenge Program for the Ethylphenols Category.

This submission is also being sent electronically in Adobe Acrobat pdf format to the following e-mail addresses:

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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. Mark Townsend (w/attachment) (via e-mail)

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

CATEGORY ANALYSIS DOCUMENT AND UPDATED CATEGORY JUSTIFICATION AND TEST PLAN

ETHYLPHENOL ISOMERS

Submitted by:
MERISOL USA LLC
Houston, Texas

May 2006

INTRODUCTION

On May 12, 2003, Merisol USA LLC (Merisol) submitted a Category Justification and Test Plan for ethylphenols isomers. The Category consisted of all three structural isomers of ethylphenol and is described in detail below. Testing that was conducted following the 2003 submission consists of the following:

Acute algae toxicity
Acute Daphnia toxicity
Biodegradation
Bacterial mutation
In vitro mammalian cell chromosome aberration
Mammalian acute oral toxicity
Mammalian repeated-dose toxicity and reproductive/developmental toxicity.

The results of these tests are summarized in Appendix A -- ROBUST SUMMARY FOR MIXED ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOLS CATEGORY. As with the methyl phenol (cresols) series of isomers, the isomers of ethylphenol exhibit related toxicity based on the similarity of their structure. Thus, the additional testing conducted further supports the Ethylphenols Category.

Ethvluhenols

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 204.5°C, 2 180°C and 2 18.4°C, 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.' Isolation of the o-ethylphenol isomer by distillation is possible, but has not proved to be commercially viable.

Exnosure Pattern for the Ethvlphenols

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]

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. The Merisol product containing all three ethylphenol isomers that is sold in the greatest volume and that contains the highest percentage of ethylphenol isomers is WES 297. This product contains 18.5% ethylphenols, the highest percentage in any Merisol product containing ethylphenol isomers.

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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.

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

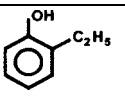
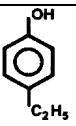
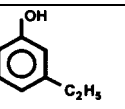
Ethylnhenols

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 defines ethylphenols as a mixture containing portions of ethylphenol isomers normalized to match the ratios of ethylphenol isomers occuring in an actual commercial product containing the highest percentage of all three ethylphenols. The composition of the Mixed Ethylphenol Test Mixture is:

Ethylphenol Isomer	Mole % in Test Mixture
o-ethylphenol (CAS # 90006)	25.9
p-ethylphenol (CAS# 123079)	33.0
m-ethylphenol (CAS# 620 177).	41.1.

This mixture mimics worker and consumer exposure to a commercial product but allows for the study of ethylphenol isomers without confounding effects of non-ethylphenol product components. It represents 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 2.68 to 2.77 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 25°C range from 0.05 to 0.16 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 will 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 another 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 likewise to be the case for ethylphenols. New data summarized in this submission show the data for Ethylphenols.

Table 3: Ethylphenols Physical Properties

Chemical	o-Ethylphenol	p-Ethylphenol	m-Ethylphenol
CAS Registry Number	90006	123079	620177
Boiling Point	204.5°C	218.0°C	218.4°C
Melting Point	-3.3°C	45.1°C	-4°C
Octanol/Water Partition Coefficient	2.72	2.68	2.77
Water Solubilty	5340 mg/L @ 25°C	4900 mg/L @ 25°C	Slightly soluble
Vapor Pressure	0.16 mmHg@ 25°C	0.07 mmHg@ 25°C	0.05 mmHg@ 25°C
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] We describe the cresols data below because we believe that the ethylphenol isomers will act analogously based on their similar chemical/physical properties; we do not believe, however, that the data support otherwise relying on the cresols data for conclusions about mixed ethylphenols with regard to HPV testing requirements, and we do not present these data for that purpose.

Evaluation of Cresols Data

Attachment 1 to this document presents in tabular form summaries of developmental 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

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[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."

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 with ethylphenols is based on the structural similarity among this group of isomers

Evaluation of New and Existing Ecotoxicitv, Mammalian Toxicitv. and Genetic Toxicity Data for Ethvluhenols

The acute aquatic environmental toxicity of the p-ethyphenol has been characterized in a freshwater fish species. The EC_{50} value from this study was 10.4 mg/L. Recently conducted acute aquatic toxicity testing in *Daphnia* with the Mixed Ethylphenol Test Mixture resulted in an EC_{50} of 9.0 mg/L and a NOEC of 2.4 mg/L for immobilization. In acute toxicity testing of algae, the EC_{50} for increase in biomass was 17 mg/L and the EC_{50} for growth rate was >22 mg/L. These acute aquatic toxicity values for the Mixed Ethylphenol Test Mixture are very similar to the acute fish EC_{50} reported for p-ethylphenol and actually bracket the EC_{50} of 10.4 mg/L showing that ethylphenols are no more than moderately toxicity acutely and there are no important differences in acute aquatic toxicity among the isomers.

Biodegradation of each of the ethylphenol isomers has been investigated for aqueous anaerobic (o-ethylphenol) and aqueous aerobic degradation (meta- and para-ethylphenol). Complete degradation was not achieved in the tests, but 76-93 percent of the compounds were degraded aerobically within 8 weeks in an open vessel test. In closed vessel testing, the isomers in the Mixed Ethylphenol Test Mixture were degraded 73.9 percent in 7 days. There are at least two methodological differences that could account for the difference in degradation rates: (1) the earlier test was an open vessel test and the recent testing used a closed vessel; and (2) the earlier test used unacclimated soil as the degradation medium while the recent testing used activated sludge. Nevertheless, in each case the ethylphenol isomers were essentially completely degraded in the presence of air without any apparent isomer effect.

Mammalian single and repeated-dose oral toxicity were rather unremarkable. The acute oral LD_{50} in rats for the Mixed Ethylphenol Test Mixture was 980.6 mg/kg. Systemic toxicity in repeated oral dosing of rats produced clinical signs (urine staining of fur and salivation immediately following dosing) at all dose levels (30-245 mg/kg/day) but little else. There were no treatment-related body weight changes, some organ weight changes (liver) but no gross or microscopic changes in any organ or tissue, and no neurotoxicity. This is consistent in dose level and effect with the pattern of effects seen in individual isomers of cresol and in cresol isomer mixtures in which the maternal systemic NOAEL for each isomer was 175 mg/kg/day in developmental toxicity testing and 30 mg/kg/day (<30 for m-cresol) in the parental animals of a multigeneration reproduction toxicity test.

Reproductive and developmental toxicity was screened with the Mixed Ethylphenol Test Mixture and there were no treatment-related effects in these parameters at the highest dose tested, 245 mg/kg/day. This supports the contention of equal toxicity (or lack of) across all members of the Category, i.e., across all ethylphenol isomers.

Genetic toxicity testing of the Mixed Ethylphenol Test Mixture produced a negative test for mutation in bacteria (Ames test) in the presence and absence of exogenous metabolic activation and a positive in vitro test for structural but not numeric chromosomal aberration in the presence and absence of metabolic activation. Bacterial testing of each cresol isomer and of the cresol isomer mixture produced negative results for mutation when tested with and without metabolic activation. *In vitro* testing of the o- and p-cresol isomers produced structure aberration in the presence and absence of metabolic activation but m-cresol did not produce chromosomal aberrations.

The new data for the Ethylphenols Category show a pattern that was demonstrated in isomer and isomer-mixture testing of cresols, the Methylphenol analogue of Ethylphenol. That pattern suggests that within the isomeric family there is little difference in toxicity, ***i.e.,*** there is no isomer effect. This pattern is supported by the lack of difference in target organs and the consistency in effect levels observed from the studies of the isomers and mixtures of the isomers. Accordingly, Merisol believes that all members of the Ethylphenols Category have equivalent general toxicity and that separate testing of isomers is not required.

CATEGORY TEST PLAN

Merisol believes that existing and newly submitted data for physiochemical properties, photodegradation, biodegradation, acute and repeated-dose mammalian toxicity, reproductive toxicity, genetic toxicity and ecotoxicity are sufficient for addressing these endpoints for the HPV Challenge Program. As noted in previous versions of this test plan, Merisol has not performed hydrolysis testing, which is not appropriate for these substances, and is not determining fugacity endpoint, which is fulfilled by modeling and cannot be run appropriately with mixtures. Accordingly, Merisol has conducted the studies listed in Table 5 using the Mixed Ethylphenol Test Mixture (composition shown below) to supply data for SIDS endpoints in the Ethylphenols Category.

Ethylphenol Isomer	Mole % in Test Mixture
o-ethylphenol (CAS # 90006)	25.9
p-ethylphenol (CAS# 123079)	33.0
m-ethylphenol (CAS# 620 177).	41.1.

This mixture represents 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.

CONCLUSION

Ethylphenol mixtures sold or distributed in the U.S. by Merisol are of variable composition. Testing every possible variation would have violated animal use goals without

producing additional meaningful scientific information, and would thus also have been unnecessarily burdensome. Because exposure of people and the environment is to mixtures of ethylphenols, data were developed on a mixture of three ethylphenols and those data have provided cogent and reliable information for assessment of the potential hazards that ethylphenol-containing products may present to humans and the environment. The approach used accounts for any interactions between ethylphenol isomers that may impact toxicity. Testing of the Mixed Ethylphenol Test Mixture to support the Ethylphenols Category shows a pattern that was also demonstrated in isomer and isomer-mixture testing of cresols, the methylphenol analogue of ethylphenol. That pattern suggests that within the isomeric family there is little difference in toxicity, ***i.e.,*** there is no isomer effect. This pattern is supported by the lack of difference in target organs and the consistency in effect levels observed from the studies of the isomers and mixtures of the isomers. Accordingly, Merisol believes that all members of the Ethylphenols Category have equivalent general toxicity and that separate testing of isomers is not required.

Table 5: Ethylphenols Category HPV Test Plan and Data Matrix

HPV DATA ENDPOINT	DATA DEVELOPMENT METHOD AND TEST SUBSTANCE	TESTING RESULTS
1. ENVIRON-MENTAL FATE		
Biodegradation	Aqueous Aerobic; Water column passed through acclimated soil m-Ethylphenol	93% removeal in 37 days
Biodegradation	Aqueous Anaerobic; Groundwater column inoculated into anaerobic chamber o-Ethylphenol	23-42% removal in 8 weeks
Biodegradation	Aqueous Aerobic; Water column passed through acclimated soil p-Ethylphenol	76% removeal in 37 days
Biodegradation	OECD Test Guideline 301 Ethylphenols Mixed Isomers	Mean biodegradation at study termination was 87.0% of theoretical. At day 7, ethylphenols were 73.9% degraded. Ethylphenols are readily degradable
2. HEALTH EFFECTS		
Acute Toxicity	Acute Oral Toxicity: OECD Health Effects Test Guideline 425 Ethylphenols Mixed Isomers	The Acute oral LD50 = 980.62 mg/kg and the NOAEL = 175 mg/kg at post-dose 14.
Repeat Dose Toxicity	Combined Repeat-Dose Toxicity Study with Reproductive/ Developmental Toxicity Screen: OECD Health Effects Test Guideline 422 Ethylphenols Mixed Isomers	The NOAEL for the study was <30 mg/kg/day because of clinical observations at all dose levels (salivation and urine-stained fur). The reproductive NOAEL was >245 mg/kg/day.
Repro-Develop. Toxicity		
Genetic Toxicity	Bacterial Mutation Test: OECD Health Effects Test Guideline 471 Ethylphenols Mixed Isomers	The test material was negative for mutation in the presence and absence of exogenous metabolic activation.
	In vitro chromosomal aberration test OECD Guideline 473 Ethylphenols Mixed Isomers	The percentage of cells with structural aberrations was significantly increased with and without exogenous metabolic activation. Treatment-related increases in numeric aberrations were not produced.
3. ECOTOXICITY		
Fathead Minnow	Acute Aqueous Toxicity; Flow-through Exposure p-Ethylphenol	LC50 = 10.4 mg/L
Daphnia	Acute Toxicity to Aquatic Invertebrates: OECD Test Guideline 202 Ethylphenols Mixed Isomers	Immobilization of daphnids The 48-hour EC50 = 9.0 mg/L (6.2-12 mg/L) 48-hour growth rate NOEC = 2.4 mg/L
Algae	Acute Toxicity to Aquatic Plants (Algae): OECD Test Guideline 201 Ethylphenols Mixed Isomers	Total biomass EC50 = 17 mg/L (14-19 mg/L) 72-hour biomass NOEC = 5.2 mg/L Growth rate EC50 >22 mg/L 72-hour growth rate NOEC = 5.2 mg/L

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 I

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	NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	NOAEL = 5 mg/kg/day Maternal LOAEL = 50 mg/kg/day Hypoactivity, audible respiration and ocular discharge. No other signs or changes.	Maternal NOAEL = 5 mg/kg/day Maternal LOAEL = 50 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	Developmental NOAEL = 50 mg/kg/day No embryotoxicity or fetotoxicity. Skeletal variations observed in high-dose pups (100mg/kg/day)	Developmental NOAEL= 100 mg/kg/day No embryotoxicity or fetotoxicity.	Developmental NOAEL = 100 mg/kg/day No embryotoxicity or fetotoxicity.
Rat Oral Gavage Developmental Toxicity: Maternal NOAEL & Effect/Target Organ	Maternal NOAEL 175 mg/kg/day Maternal LOAEL = 450 mg/kg/dayHypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 16% mortality.	Maternal NOAEL = 175 mg/kg/day Maternal LOAEL = 450 mg/kg/day Hypoactivity, audible respiration, ataxia, twitches, tremors, decreased food consumption and body weight gain, 0% mortality.	Maternal NOAEL =175 mg/kg/day Maternal LOAEL = 450mg/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	Developmental NOAEL = 175 mg/kg/day No increase in malformations, visceral variations at the high-dose.	Developmental NOAEL= 450 mg/kg/day No increase in malformations. No increase in variations.	Developmental NOAEL = 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	Parental NOEAL 30 mg/kg/day Parental LOAEL = 175 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 FO and F 1 adult necropsy.	Parental NOAEL <30 mg/kg/day Effects included high-dose mortality (450mg/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 FO and Fl parents.	Parental NOAEL = 30 mg/kg/day Parental LOAEL 175mg/\kg/day. High-dose mortality (450mg/.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 FO 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	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in Fl or F2 pups.	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in Fl or F2 pups.	F1 and F2 NOAEL = 175 mg/kg/day No gross lesions in Fl or F2 pups.

SUMMARY OF CRESOLS MUTAGENICITY DATA

ASSAY / TEST SUBSTANCE	ORTHO	META	PARA	MIXED
GENE MUTATION				
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

Develonmental Toxicity and Reproductive Toxicitv References:

R. W. Tyl, Unpublished Report Number 5 l-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 5 l-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 5 l-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 5 1-614: "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 5 l-5 12: "Two Generation Reproduction Study of p-Cresol, Administered by Gavage to Sprague-Dawley Rats," Bushy Run Research Center, Export, Pa., March 28, 1989.

Genetic Toxicitv 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 13 19-77-3, European Chemicals Bureau, March 1, 2001.

APPENDIX A
ROBUST SUMMARIES FOR MIXED ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOLS CATEGORY

Robust Summary – ETHYLPHENOLS

Algal toxicity

TEST SUBSTANCE	
Identity	Ethylphenol Isomer Mixture — Mole % in Test Mixture
	o-ethylphenol (CAS # 90006) — 25.9
CAS #	p-ethylphenol (CAS# 123079) — 33.0
	m-ethylphenol (CAS# 620177). — 41.1.
Remarks	Test substance was a mixture of ethylphenol isomers blended as indicated above. Lot number 13 JAN2004 99.8 1% purity
METHOD	
Method/guideline	OECD Guideline 201 Alga, Growth Inhibition Test (OECD, 1984)
Type (test type)	Static acute
GLP	**Yes**
Year	2005
Species	*Psuedokirchnerielle subcapitata*
Analytical monitoring	Yes, GC/FID analysis on samples collected at 0 and 72 hours
Exposure period	72 hours
Statistical methods	**Yes**
Test conditions	Closed system, 72-hour duration, temperature range 22-24°C, continuous illumination at 7000 to 8300 lux (650 to 775 footcandles), shaking rate 100 rpm. Triplicate algal cultures used for each treatment level. Five treatment levels, negative, solvent and three analytical QC control groups. Test exposure levels were based on pilot testing; actual test concentrations were 0, 1.1, 2.0, 5.2, 16 and 22 mg/L. pH was 8.2 at study initiation and 9.4 to 9.9 at 72 hours. Cell number was measured at 24, 48, and 72 hours.
RESULTS	
Concentration	0, 1.1, 2.0, 5.2, 16 and 22 mg/L Mean measured
Endpoint criteria	Inhibition of total biomass (area under growth curve) and average growth rate relative to control
EC_{50}	Total biomass EC_{50} = 17 mg/L (14-19 mg/L) 72-hour biomass NOEC = 5.2 mg/L Growth rate EC_{50} >22 mg/L 72-hour growth rate NOEC = 5.2 mg/L
DATA QUALITY	
Reliability	(1) Reliable without restrictions

REFERENCES	Ethyl Phenols Acute Toxicity to the Freshwater Green Alga, *Psuedokirchneriella subcapitata.*, Springborn Smithers Laboratory Report 13824.6105, Wareham, MA. June 7, 2005

Daphnia toxicity

TEST SUBSTANCE	
Identity	Ethylphenol Isomer Mixture — Mole % in Test Mixture o-ethylphenol (CAS # 90006) — 25.9
CAS #	p-ethylphenol (CAS# 123079) — 33.0 m-ethylphenol (CAS# 620 177). — 41.1.
Remarks	Test substance was a mixture of ethylphenol isomers blended as indicated above. Lot number 13 JAN2004 99.8 1% purity
METHOD	
Method/guideline,	OECD Guideline 202 Daphnia sp. Acute Immobilization Test (OECD, 1984)
Type (test type)	Static, acute
GLP	**Yes**
Year	2005
Species	*Daphnia magna*
Analytical monitoring	Yes, GC/FID analysis on samples collected at 0 and 48 hours
Exposure period	48 hours
Statistical methods	**Yes**
Test conditions	Closed system, 48-hour duration, temperature range 19-20°C. Four replicate vessels with five daphnids each were used for each treatment level. Five treatment levels, negative, solvent and three analytical QC control groups. Test exposure levels were based on pilot testing; actual test concentrations were 0, 1.9, 2.4, 6.2, 12 and 27 mg/L. pH was 8.0 at study initiation. Specific conductance was 500 µmhos/cm; total hardness (as $CaCO_3$) was 190 mg/L total alkalinity (as $CaCO_3$) was 120 mg/L. Preliminary testing indicated that volatilization of ethylphenols test material could be controlled with closed test vessels.
RESULTS	
Concentration	0, 1.9, 2.4, 6.2, 12 and 27 mg/L Mean measured
Endpoint criteria	Immobilization of daphnids
EC_{50}	The 48-hour EC_{50} = 9.0 mg/L (6.2-12 mg/L) 48-hour growth rate NOEC = 2.4 mg/L
DATA QUALITY	
Reliability	(1) Reliable without restrictions

REFERENCES	Ethyl Phenols Acute Toxicity to the Water Fleas, *Daphnia* magna, Under Static Conditions. Springborn Smithers Laboratory Report 13824.6106, Wareham, MA. June 7, 2005

Biodegradation

TEST SUBSTANCE	
Identity	Ethylphenol Isomer Mixture — Mole % in Test Mixture
	o-ethylphenol (CAS # 90006) — 25.9
CAS #	p-ethylphenol (CAS# 123079) — 33.0
	m-ethylphenol (CAS# 620 177). — 41.1.
Remarks	Test substance was a mixture of ethylphenol isomers blended as indicated above. Lot number 13 JAN2004 99.8 1% purity
METHOD	
Method/guideline	ASTM E 1720-95 Sealed Vessel for CO_2 Evolution Biodegradation Test; ISO/DIS-14593 Headspace and OPPTS 835-120 CO_2 Evolution Biodegradation Test
Type (test type)	Test vessels incubated aerobically in dark for 28 days. This method permitted testing of water soluble and insoluble plus volatile compounds
GLP	**Yes**
Year	2004
Species	Activated sludge
Analytical monitoring	Headspace total inorganic carbon (CO_2) determined 7, 10, 14, 21 and28
Exposure period	28 days
Statistical methods	**Yes**
Test conditions	20 mL glass capped vials maintained for 28 days in the dark at 22±2°C, vessels were swirled on days 2, 5, 7, 14, 21 and 28. 27 vials contained test substance, 27 vials contained reference substance (sodium benzoate) and 27 vials were used as inoculum control. Preliminary testing indicated that volatilization of ethylphenols test material could be controlled with closed test vessels.
RESULTS	
Endpoint criteria	Evolution of CO_2 in vessel headspace. Sodium benzoate reference material ws rapidly and extensively degraded (>60% in 10 days). The mean biodegradation value for ethylphenols at study termination was 87.0% of theoretical. At day 7, ethylphenols were 73.9% degraded.
Conclusion	Ethylphenols are readily degradable.
DATA QUALITY	
Reliability	(1) Reliable without restrictions

REFERENCES	Ethyl Phenols: Determination of the Biodegradability of a Test Substance. Springborn Smithers Laboratory Report 13824.6107, Wareham, MA. October 14, 2004

Bacterial Mutation Test

TEST SUBSTANCE	
Identity	Ethylphenol Isomer Mixture — Mole % in Test Mixture
	o-ethylphenol (CAS # 90006) — 25.9
CAS #	p-ethylphenol (CAS# 123079) — 33.0
	m-ethylphenol (CAS# 620177). — 41.1.
Comments	Test substance was a mixture of ethylphenol isomers blended as indicated above. Lot number 13JAN2004 99.8 1% purity
METHOD	
Method/guideline	OECD Guideline 47 1 Bacterial Reverse Mutation Test
Type (test type)	Plate incorporation with and without exogenous metabolic activation (Aroclor 1254-induced rat liver S-9) five *Salmonella typhimurium* strains (TA 98, TA 100, TA1535, TA 1537) and *Escherichia coli* WP2 uvrA
GLP	**Yes**
Year	2004
Analytical monitoring	**No**
Exposure period	48-72 hours
Statistical methods	Mean and Std Dev of revertant counts
Test conditions	Preliminary testing included test material solubility and cytotoxicity (dose range finding). Condition of background lawn was evaluated prior to mutagenicity testing. Test, positive and negative control cultures were plated in triplicate. DMSO was used as a solvent for the test material. Five test concentrations ranging from 50 to 5000 µg/plate were evaluated.
RESULTS	
Concentration	50, 150, 500, 1500 and 5000
Units	µg test material/plate
Conclusion	Toxicity as observed at 1500 and 5000 µg/plate. No test material precipitation was observed. The test material was negative for mutation in the presence and absence of exogenous metabolic activation.
DATA QUALITY	
Reliability	(1) Reliable without restrictions
REFERENCES	Bacterial Reverse Mutation Assay: Ethyl Phenols. BioReliance Laboratory, Rockville, Md., Study Number AA89JS.502.BTL, November 1, 2004.

***In Vitro* Mammalian Chromosome Aberration Test**

TEST SUBSTANCE	
Identity	Ethylphenol Isomer Mixture — Mole % in Test Mixture o-ethylphenol (CAS # 90006) — 25.9 p-ethylphenol (CAS# 123079) — 33.0 m-ethylphenol (CAS# 620 177). — 41.1.
CAS #	
Comments	Test substance was a mixture of ethylphenol isomers blended as indicated above. Lot number 13JAN2004 99.8 1% purity
METHOD	
Method/guideline	OECD Guideline 473 *In* Vitro Mammalian Cell Chromosome Aberration Test; Evans, et al., (1976) Cytological methods for detecting chemical mutagens, in A. Hollaender (Ed.) Chemical Mutagens, Principles and Methods for their detection, Vol.4, Plenum Press, NY.; Galloway, et al., (1994) Report from working group on in ***vitro*** tests for chromosome aberrations, Mutation Research 3 12 (3): 241-246
Type (test type)	Chinese hamster ovary (CHO) cells with and without exogenous metabolic activation (Aroclor 1254-induced male rat liver S-9) evaluated for numerical and structural aberration
GLP	**Yes**
Year	2004
Analytical monitoring	**No**
Exposure period	Non-activated cultures: 4 and 20 hours; activated cultures: 4 hours
Statistical methods	Number and types of chromosome aberrations scored and analyzed using Fisher's exact test and, if positive in the Fisher's test, Co&ran-Armitage test was used to measure dose-responsiveness.
Test conditions	Preliminary testing included test material solubility and cytotoxicity (nine concentrations) with and without S-9. Test, positive and negative control cultures were cultured in duplicate. DMSO was used as a solvent for the test material. Three to eight test concentrations were employed depending on exposure time (4 or 20 hours) or presence or absence of S-9. Mitotic index was determined to ensure adequate number of metaphase cells. A minimum of 200 metaphase spreads were examined for chromatid and chromosomal structural or numerical aberrations. Chromatid gaps were scored but not included in analysis.
RESULTS	
Conclusion	Precipitate was observed in culture medium at test material concentrations of ≥1500 µg/mL. Based on cell growth inhibition at test material concentrations at 0.5, 50 and 1500 µg/mL in nonactivated 4-hour cultures and

	≥1500 µg/mL in the S-9 4-hour cultures, and concentrations >150 µg/mL in the 20-hour exposure, test dose levels were 50 - 1200 µg/mL for S-9 activated and nonactvated 4-hour exposures and 5 - 120 µg/mL for 20-hour exposures. Additional testing for activated 4-hour cultures was conducted at 100,200 and 120 µg/mL. The percentage of cells with structural aberrations was significantly increased by 4- and 20-hour treatment without exogenous metabolic activation and in the 4-hour exposure with S-9 activation. Treatment-related increases in numeric aberrations were not produced in this study with ethylphenols.
DATA QUALITY	
Reliability	(1) Reliable without restrictions
REFERENCES	*In* Vitro Mammalian Chromosome Aberration Test: Ethyl Phenols. BioReliance Laboratory, Rockville, Md., Study Number AA89JS.331.BTL, November 3, 2004.

Mammalian acute toxicity

TEST SUBSTANCE	
Identity	Ethylphenol Isomer Mixture — Mole % in Test Mixture o-ethylphenol (CAS # 90006) — 25.9 p-ethylphenol (CAS# 123079) — 33.0
CAS #	m-ethylphenol (CAS# 620 177). — 41.1.
Remarks	Test substance was a mixture of ethylphenol isomers blended as indicated above. Lot number 13 JAN2004 99.8 1% purity
METHOD	
Method/guideline	OECD Guideline 425, Acute Oral Toxicity – Up and Down Procedure (December 200 1)
Type (test type)	Acute oral gavage
GLP	Yes
Year	2005
Species	Female Sprague-Dawley rat
Analytical monitoring	**Yes**
Exposure period	Single exposure, 14-day post-exposure observation period
Statistical methods	Yes, averages and proportions calculated on body weight gain and survival
Test conditions	Single, oral gavage dosing of test material to overnight fasted rats. Corn oil was the vehicle. Animals observed for clinical observations (7 times daily on day of dosing) and viability (twice daily), body weight and food consumption were recorded daily, gross necropsy at sacrifice.

RESULTS	I
Concentration	175,550 or 1750 mg/kg
Endpoint criteria	Mortality Nine animals were tested. Mortality occurred in three animals, all in the high-dose group. Clinical observations included lacrimation, excess salivation, and urine-stained fur in the mid- and top-dose group. High-dose animals developed decreased motor activity, twitching behavior, prostration, ptosis, ataxia impaired righting reflexes and limb use, and tachypnea. Signs developed rapidly following dosing and disappeared by day 7 post-dosing. Weight-gain and feed consumption were affected by treatment.
LD_{50}	The Acute oral LD_{50} = 980.62 mg/kg and the NOAEL = 175 mg/kg at post-dose 14.
DATA QUALITY **Reliability**	(1) Reliable without restrictions
REFERENCES	Acute Oral Toxicity Study of Ethyl Phenols in Rats – Up and Down Procedure. CR-DDS Argus Division Report 37 13-002, Horsham, PA., March 16, 2005

Mammalian repeated-dose toxicity
Reproductive/developmental toxicity

TEST SUBSTANCE	
Identity	Ethylphenol Isomer Mixture — Mole % in Test Mixture o-ethylphenol (CAS # 90006) — 25.9 p-ethylphenol (CAS# 123079) — 33.0
CAS #	m-ethylphenol (CAS# 620 177). — 41.1.
Remarks	Test substance was a mixture of ethylphenol isomers blended a indicated above. Lot number 13 JAN2004 99.8 1% purity
METHOD	
Method/guideline	OECD Guideline 422, Combined Repeated-Dose Toxicity Study with the Reproductive/Developmental Toxicity Screening Test (March 1996)
Type (test type)	Repeated-dose, oral gavage
GLP	Yes
Year	2005
Species	Female Sprague-Dawley rat
Analytical monitoring	Yes, GC/FID analysis of dosing preparation concentration, stability and homogeneity.
Exposure period	28 days for males; 54 days for females
Statistical methods	Yes, body weight, weight gains and reproductive endpoints analyzed by ANOVA and Dunnett's. Reproductive data analyzed by Fisher's exact.

Test conditions	Ten adult male and 10 female rats per group, three test and one control group, received test material or vehicle orally by gavage daily for at leas 28 days (males) or 54 days (females). Dosing before and during mating, during gestation and for days l-5 of lactation. Observations for viability, clinical signs of toxicity, food consumption and body weight gain, functional observational battery and motor activity, hematology, clinical chemistry, developmental toxicity and reproductive performance, gross and microscopic post-mortem examination.
RESULTS **Concentration** **Endpoint criteria**	0, 30, 100 or 245 mg/kg/day Systemic toxicity in adult male and female rats; reproductive performance; developmental toxicity, neurotoxicity. All rats survived treatment. In males, urine staining of fur was seen at all treatment levels. Body weight gain and food consumption was reduced at all dose levels. Mating frequency was unaffected by treatment. Neurotoxicity (motor activity and FOB) was not produced by treatment; there were no treatment-related effects seen at gross necropsy or histopathologically. In females, salivation was seen following dosing at all treatment levels. Body weight gain and food consumption during pre-mating, mating, gestation and lactation were unaffected by treatment. Mating and fertility were unaffected by treatment. Pup viability was unaffected by treatment. F 1 animals showed no clinical or necropsy signs related to treatment of pregnant dams. Neurotoxicity (motor activity and FOB) was not produced by treatment; there were no treatment-related effects seen at gross necropsy or histopathologically.
NOAEL	The NOAEL for the study was <30 mg/kg/day because of clinical observations at all dose levels (salivation and urine-stained fur). The reproductive NOAEL was > 245 mg/kg/day.
DATA QUALITY **Reliability**	(1) Reliable without restrictions
REFERENCES	Oral (gavage) Combined Repeated-Dose Toxicity Study of Mixed Xylenols and Ethyl Phenols with the Reproductive/Developmental Toxicity Screening Test. CR-DDS Argus Division Report 3713-003, Horsham, PA., November 22, 2005

(1) Klimisch, H. J., M. Andreae, and U. Tillmann. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. Regulatory Toxicol. and Pharmacol. 25: l-5.

APPENDIX B
ROBUST SUMMARIES FOR m-ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
m-Ethylphenol (CAS 620-17-7)

Type	: Melting Point
Value	: -4.0 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: 1955 or earlier
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Terres, *Brennstoff Chemie*,36,272 (1955)

Type	: Boiling Point
Value	: 218.42 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: Unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type	: Vapor Pressure
Value	: 0.05 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: Unknown
Year	: Unknown
Remarks	: None
Quality	: Estimated < 5% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR values regressed from seven literature references.

Type	: Partition Coefficient
Value	: Log Kow = 2.77
Method	: unknown
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Water Solubility
Value	: 2.3 wt % at 127.3 °C
Method	: Unknown
GLP	: Unknown
Year	: 1955 or earlier
Remarks	: Expected to be slightly soluble @ 25°C
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(5) Terres, *Brennstoff Chemie*, 36,272 (1955)

Type	: pKa Value
Value	: 10.17 @ 20°C
Method	: unknown
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(6) Ullmann's Encyclopedia of Industrial Chemistry (1985), Vol. Al 9, p. 323

ENVIRONMENTAL FATE ELEMENTS
m-Ethylphenol (CAS 620- 17-7)

Type	: Atmospheric fate
Value	: T1/2 = 5 hours
Method	: Structure activated method
GLP	: unknown
Year	: 1993
Remarks	: Vapor-phase m-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 8.4x10S-11 cc/molecule-set @ 25°C
Quality	: unknown
Reliability	: (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous aerobic degradation
Value	: 93% removal in 37 days
Method	: Water column passed through acclimated soil
GLP	: Unknown
Year	: 1989
Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX C
ROBUST SUMMARIES FOR o-ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
o-Ethylphenol (CAS 90-00-6)

Type	: Melting Point
Value	: -3.3 °C
Decomposition	: No
Sublimation	: No
Method	: Unknown
Year	: 1963 or earlier
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR value taken from Biddescombe, *J. Chem. Soc.* ,5764, (1963)

Type	: Boiling Point
Value	: 204.5 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: Unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type	: Vapor Pressure
Value	: 0.16 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: Estimated < 5% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) 1999, DIPPR values regressed from nine literature references.

Type	: Partition Coefficient
Value	: Log Kow = 2.72
Method	: unknown
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Water Solubility
Value	: 5340 mg/L @ 25°C
Method	: Uknown
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(5) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: pKa Value
Value	: 10.47 @ 20°C
Method	: unknown
GLP	: unknown
Year	: Unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(6) Ulhnann's Encyclopedia of Industrial Chemistry (1985), Vol. A19, p. 323

ENVIRONMENTAL FATE ELEMENTS
o-Ethylphenol (CAS 90-00-6)

Type	: Atmospheric fate
Value	: T1/2 = 9 hours
Method	: Structure estimated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase o-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 4.2 x 10E-11 cc/molecule-set @ 25°C
Quality	: unknown
Reliability	: (4) Not Assignable

(7) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous anaerobic degradation
Value	: 23-42% removal in 8 weeks
Method	: Groundwater column inoculated into anaerobic digestor
GLP	: Unknown
Year	: 1983
Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(8) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX D
ROBUST SUMMARIES FOR p-ETHYLPHENOL STUDIES SUPPORTING THE ETHYLPHENOLS CATEGORY

PHYSICAL-CHEMICAL ELEMENTS
p-Ethylphenol (CAS 123-07-g)

Type	: Melting Point
Value	: 45.08°C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: unknown
GLP	: Unknown
Remarks	: None
Quality	: Estimated < 5% error
Reliability	: (2) Reliable with restrictions

(1) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type	: Boiling Point
Value	: 217.99 °C
Decomposition	: No
Sublimation	: No
Method	: unknown
Year	: unknown
GLP	: unknown
Remarks	: None
Quality	: Estimated < 1% error
Reliability	: (2) Reliable with restrictions

(2) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR value taken from Texas A&M Thermodynamics Research Center "Selected Values of Properties of Chemical Compounds", 1980.

Type	: Vapor Pressure
Value	: 0.07 mmHg at 25°C
Method	: Calculated from vapor pressure constants in reference
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: Estimated < 10% error
Reliability	: (2) Reliable with restrictions

(3) Design Institute for Physical Property Data (DIPPR) Revised 2000, DIPPR values regressed from three literature references.

TYPE	: Partition Coefficient
Value	: Log Kow = 2.68
Method	: Unknown
GLP	: Unknown
Year	: unknown
Remarks	: None
Quality	: Unknown
Reliability	: (2) Reliable with restrictions

(4) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Log Kow
Value	: 2.66 / 2.81
Method	: Unknown / Calculated
GLP	: unknown / unknown
Year	: Unknown / Unknown
Remarks	: None / None
Quality	: Unknown / Unknown
Reliability	: (2) Reliable with restrictions

(5) Verschueren, "Handbook of Environmental Data on Organic Chemicals"

Type	: Water Solubility
Value	: 4900 mg/L @ 25°C
Method	: Uknown
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(6) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: pKa Value
Value	: 10.38 @ 20°C
Method	: Unknown
GLP	: unknown
Year	: unknown
Remarks	: None
Quality	: unknown
Reliability	: (2) Reliable with restrictions

(7) Ulhnann's Encyclopedia of Industrial Chemistry (1985), Vol. A19, p. 323

ECOTOXICITY ELEMENTS
p-Ethylphenol (CAS 123-07-9)

Type	: Acute
Species	: Fathead minnow
Sex	: Not stated
Strain	: Not applicable
Route of administration	: Flow-through
Exposure period	: 96hr
Frequency of treatment	: One day
Post exposure period	: Not applicable
Doses	: 0, 10.5, 16.1, 24.8, 38.2 and 58.9 mg/l, analytical verification
Control group	: Untreated
LC_{50}	: 10.4 mg/l
Method	: Evaluate test water quality, fish behavior and pharmacotoxic signs, body weight and survival.
Year	: 1985
GLP	: Not stated
Test substance	: 4-ethylphenol 99% pure
Reliability	: (2) Reliable with restrictions

(8) Geiger, D. L., et al., Acute toxicities of organic chemicals to fathead minnows, Vol. III. Center for Lake Superior Environmental Studies, U. of Wisciensin - Superior. US EPA Cooperative Agreements Superior, WI., p 195, 1985.

ENVIRONMENTAL FATE ELEMENTS
p-Ethylphenol (CAS 123-07-9)

Type	: Atmospheric fate
Value	: T1/2 = 9 hours
Method	: Structure estimated method
GLP	: Unknown
Year	: 1993
Remarks	: Vapor-phase p-ethylphenol was degraded in the atmosphere by reaction with photochemically produced hydroxyl radicles Reaction rate constant = 4.2 x 10E-11 cc/molecule-set @ 25°C
Quality	: Unknown
Reliability	: (4) Not Assignable

(9) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

Type	: Aqueous aerobic degradation
Value	: 76% removal in 37 days
Method	: Water column passed through acclimated soil
GLP	: Unknown
Year	: 1989

Remarks	: Laboratory study
Quality	: unknown
Reliability	: (4) Not Assignable

(10) National Library of Medicine Hazardous Substances Data Base; May 8, 2002

APPENDIX E
ROBUST SUMMARIES FOR m-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOLS 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.:II-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

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	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	13w
Frequency of treatm.	once daily
Post exposure period	I 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

35

Strain	:	other: CD
Route of admin.	:	Gavage
Exposure period	:	13w
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
M e t h o d	:	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

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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%

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 ,1 7,1975; Clive, Mutation Res. 59,61 ,1 979, 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

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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%

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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.

5.6.2 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

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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 O-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-l 0; 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-l 2; 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)

43

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 FI-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 FO-, 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 F
ROBUST SUMMARIES FOR p-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOLS 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 bwlday):

	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

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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

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(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. TA1 00
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

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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, TA1 538
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

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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	:	pCresol 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, piloerectjon 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
Prematlng exposure period		

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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 pcresol 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 FO 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 FO 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: 2/4/1 3/6; F2 pups: O/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

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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 mglkg 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 mglkg 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 mglkg 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 pcresol 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 G
ROBUST SUMMARIES FOR o-CRESOL TOXICITY STUDIES SUPPORTING THE ETHYLPHENOLS 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 mglkg bw
LOAEL	: 242-256 mglkg 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

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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

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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

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(1)

Type	:	Repeat dose
Species	:	Mouse
S e x	:	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 histopathotogical 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)

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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/piate 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 ceils were observed in the 20 hour assay with metabolic activation at 301 and 601 ug/mi.
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 pcresol 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

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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

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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 bwlday; 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 FO 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 FO 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) mglkglday 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: O/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 mglkg bw
NOAEL teratogen.	= 175 mglkg 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 mglkg 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 mglkg bw
NOAEL developmental	50 mglkg 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 H
ROBUST SUMMARIES FOR MIXED CRESOL ISOMERS TOXICITY STUDIES SUPPORTING THE ETHYLPHENOLS 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

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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

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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
G L P : Yes
Test substance : m/p-cresol, 60%-40% mix TS: purity > 98%

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Reliability : (1) valid without restriction

(1)

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