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

CATEGORY JUSTIFICATION AND TEST PLAN

XYLENOL ISOMERS

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INTRODUCTION

Mixed Xylenols

Xylenols are liquids or crystals recovered from petroleum streams, coal coking operations and coal gasification. Several isomers are also produced synthetically. Xylenols are isomeric forms of dimethyl phenol containing two methyl groups attached to the ortho, meta, or para positions of the phenol ring. There are six possible isomeric forms of xylenol: 2,3-xylenol; 2,4-xylenol; 2,5-xylenol; 2,6-xylenol; 3,4-xylenol; and 3,5-xylenol. The boiling point range for these isomers is 201.0ºC to 227ºC.

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 xylenol isomers by distillation is not possible.[1]

Exposure Pattern for Mixed Xylenols

Merisol sells pure phenol, o-cresol, m-cresol and p-cresol. These are also sold in blends, as are the mixtures of xylenols and ethylphenols. The vast majority of xylenols and ethylphenols that Merisol produces and sells are contained in mixtures.[2] Therefore, public (and employee) exposure, as well as potential environmental exposures to Merisol's products, are primarily to blends and mixtures containing xylenols and/or ethylphenols. Because these Merisol products are generally moved into commerce as starting materials for further chemical processing, there is little consumer exposure to xylenols and ethylphenols. Merisol is by far the major, if not sole,

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[1] For the same reason, as discussed in Merisol's concurrently submitted proposal for ethylphenols, isolation of all pure m- and p-ethylphenols by distillation is not possible. Isolation of the o-ethylphenol isomer by distillation is possible, but has not proved to be commercially viable.

[2] Merisol is selling quantities of 3,4-xylenol that total 16,000 pounds, well below the HPV 1 million pound threshold. This 16,000 pounds is a portion of a 35,000 pound batch toll produced in Europe for Merisol more than three years ago as a developmental project.

U.S. producer of xylenols except for 2,6-xylenol (which is already the subject of a SIDS dossier).[3]

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. Xylenols, as well as ethylphenols, phenol, and cresols, are not components of every Merisol product mixture.

A breakdown of numbers of xylenol isomers contained in product mixtures is given in Text Table 1. Table 1 illustrates that Merisol products containing xylenol isomers (other than 2,6-xylenol which is already the subject of a SIDS dossier) include two to six different isomers in the products and that more than 60% of the xylenol products sold by Merisol have five or six xylenol isomers.

Table 1: Distribution of Individual Xylenol Isomers
In Merisol Products

	Number of Different Xylenol Isomers Present as Components In Merisol Products					
	1 xylenol isomer in product*	2 xylenol isomers in product	3 xylenol isomers in product	4 xylenol isomers in product	5 xylenol isomers in product	6 xylenol isomers in product
% of total xylenol placed into commerce by Merisol	0.7	34.7	2.3	0.6	34.0	27.5

* 2,6-xylenol is the xylenol in the product (SIDS dossier available for this isomer).

Accordingly, exposure to xylenols is primarily to a mixture of xylenol isomers.

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[3] Merisol has imported 3,5-xylenol in quantities less than 1 million pounds per year for use in its mixtures and has imported 35,000 pounds of 3,4-xylenol (see footnote 2). Merisol understands that one other company may have imported 2,4-xylenol in quantities over 1 million pounds per year in 1999, 2000, and 2001 and that this quantity was used as an intermediate in the production of another substance. Less than 350,000 pounds of pure 2,5-xylenol have been imported into the U.S. in 2000 and 2001. Merisol understands that small amounts (<20,000 pounds per year) of pure 2,3-xylenol may have been imported into the U.S. in 2000 and 2001.

DESCRIPTION OF THE CATEGORY

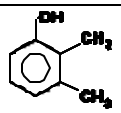
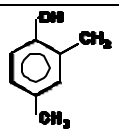
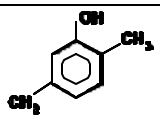
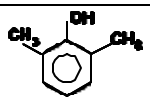
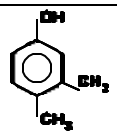
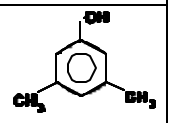
Mixed Xylenols

Each of the xylenol isomers (and an entity called "mixed xylenols") appears in the EPA HPV list of chemicals to be evaluated. Identification of the isomers is presented in Text Table 2, below. Although a CAS Registry Number has been assigned to "mixed xylenols," and mixed xylenols has been included as a test substance in the HPV Chemical Challenge Program, no definition of mixed xylenols (CAS# 1300716) is available, nor is there a single product or mixture understood by industry as "mixed xylenols." Accordingly, for purposes of the Mixed Xylenols Category, Merisol is defining mixed xylenols as a mixture containing equal portions of:

2,5-xylenol (CAS# 95874)
3,4-xylenol (CAS# 95658)
2,4-xylenol (CAS# 105679)
3,5-xylenol (CAS# 108689)
2,3-xylenol (CAS# 526750)
2,6-xylenol (CAS# 576261).

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

Table 2: Xylenols – Chemical Name, CAS Number, and Structure

Chemical:	2,3-Xylenol	2,4-Xylenol	2,5-Xylenol	2,6-Xylenol	3,4-Xylenol	3,5-Xylenol
CAS Registry Number	526750	105679	95874	576261	95658	108689
Molecular structure						

CATEGORY JUSTIFICATION

Mixed Xylenols

As structural isomers, the members of the Mixed Xylenols 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 methyl 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 2.33 to 2.36 for each of the

xylenols except 2,3-xylenol, for which no value was found. Water solubility values at 25°C are reported to range from 3450 mg/L to 7870 mg/L. These values suggest that xylenol 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 0.041 to 0.274 mmHg for the xylenols, also supporting a similar pattern of airborne distribution. Individually and as a group the xylenols are expected to exhibit low-to-moderate mobility in soil based on the $K_{o/w}$ values. Hydrolysis values have not been reported for xylenols, presumably due to the absence of a hydrolyzable functional group. Within the family of xylenol isomers, the physicochemical properties are expected to manifest similar effects on the environment and potentially on human health.

The biological response patterns of xylenols, 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 xylenols.

Table 3: Xylenols Physical Properties

Chemical	2,3-Xylenol	2,4-Xylenol	2,5-Xylenol	2,6-Xylenol	3,4-Xylenol	3,5-Xylenol
CAS Registry Number	526750	105679	95874	576261	95658	108689
Boiling Point	217.0ºC	211.0ºC	211.2ºC	201.0ºC	227.0ºC	221.8ºC
Melting Point	25ºC	24.5ºC	74.5ºC	49ºC	62.5ºC	65ºC
Density	NA	0.965 @ 20ºC	0.965 @ 20ºC	NA	0.983 @ 20ºC	0.968 @ 25ºC
Octanol/Water Partition Coefficient	NA	2.36	2.33	2.36	2.33	2.35
Water Solubility	4750 mg/L @ 25ºC	7870 mg/L @ 25ºC	3450 mg/L @ 25ºC	6050 mg/L @ 25ºC	4760 mg/L @ 25ºC	4880 mg/L @ 25ºC
Vapor Pressure	0.089mm Hg@ 25ºC	0.102mm Hg@ 25ºC	0.156mm Hg@ 25ºC	0.274mm Hg@ 25ºC	0.036mm Hg@ 25ºC	0.041mm Hg@ 25ºC
$K_{o/c}$	630	430	440	460	390	190-1400
Biodegradation	Complete in unac-climated soil 19 days	Unac-climated soil $T_{1/2}$ = 3.5days	Complete in activated sludge 5 days	Complete in unac-climated soil 4-14 days	Complete in unac-climated soil 9 days	Complete in unac-climated soil 11 days
Photodegradation in Air	$T_{1/2}$ = 4.8 hrs	$T_{1/2}$ = 5.3 hrs	$T_{1/2}$ = 4.8 hrs	$T_{1/2}$ = 5.8 hrs	$T_{1/2}$ = 4.7 hrs	$T_{1/2}$ = 3.4 hrs

NA = Not Available

Toxicological Justification for the Mixed Xylenols Category

Xylenols are dimethyl phenols. The toxicological justification for the Mixed Xylenols Category is that existing studies of structurally related compounds, methyl phenols (also known as cresols), 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.[4] 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 dimethyl phenols (xylenol isomers) based on the structural similarity among this group of isomers. The demonstration of a structure-activity relationship among the methyl phenol

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[4] 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."

isomers and the expectation of a parallel structure-activity relationship for the homolog dimethyl phenols is the toxicological justification of the Mixed Xylenols Category for HPV testing.

Toxicology of Xylenol Isomers

a. Mammalian Acute and Repeated Dose Toxicity

Mammalian toxicity testing of 2,6-xylenol, the most thoroughly tested isomer, is limited. The acute oral LD50 is reported as 1470 and 1750 mg/kg in rats (SIDS, 1997). Acute dermal penetration (LD50) studies have been completed in rats, mice and rabbits and the resulting LD50 values range from 920 to over 1500 mg/kg (SIDS, 1997). The acute inhalation LC50 in rats is reported to be >270 mg/m^3 for a 4-hour exposure, and 2,6-xylenol is reported to be a strong skin and eye irritant (SIDS, 1997). It was negative in a Guinea pig study for dermal sensitization (SIDS, 1997).

Rodent oral LD50 values for other xylenol isomers from unpublished reports (or secondary source reports) are: 444 mg/kg, 400 mg/kg, 2300 mg/kg, and 608 mg/kg for 2,5-, 3,4-, 2,4- and 3,5-xylenol, respectively.

Repeated-dose toxicity has been studied for 2,6-xylenol. In oral gavage studies ranging from 28 days to 10 months with rats and in one case, mice, 2,6-xylenol produced damage to the liver and glandular stomach. Rats tolerated 100 mg/kg/day for shorter-term exposures (28 days) but the LOAEL for a 10-month study was 6 mg/kg/day and the NOAEL was reported to be 0.06 mg/kg/day (SIDS, 1997).

A repeated dose study is reported for 2,4-xylenol in the Russian literature. The NOAEL following 90-day oral dosing in rats was 50 mg/kg/day.

b. Reproductive and Developmental Toxicity

There are no reports of reproductive toxicity studies conducted with any xylenol. An oral gavage developmental toxicity study in rats has recently been completed with the 2,6 isomer. The NOAEL for developmental toxicity was 180 mg/kg/day, based on reduction in fetal weight. The NOAEL for maternal toxicity was 60 mg/kg/day based on body weight gain suppression and decreased food consumption (SIDS, 1997).

c. Genetic Toxicity

Each of the xylenol isomers, except 2,3-xylenol, has been evaluated in bacterial mutation tests with several (but not five) Salmonella strains. The work was completed with and without exogenous metabolic activation, and was negative for gene mutation. Most of this work is published.

2,6-Xylenol is reported to be negative for gene mutation in bacterial and mammalian cell assays, with and without exogenous metabolic activation (SIDS, 1997). *In vitro* cytogenetics

testing with V79 cells produced signs of chromosomal aberration; *in vivo* testing (rat bone marrow, oral gavage) was negative for chromosome effects, including aberration (SIDS, 1997).

d. Environmental Toxicity

The acute aquatic environmental toxicity of the xylenols has been characterized in several marine and freshwater fish and invertebrate species using static and flowthrough exposure procedures. The EC50 values issuing from these studies range from 3 to 27 mg/L for fish and 10 to 16.5 mg/L for daphnia. These values are from unpublished studies or secondary sources. An algal test and a biodegradation evaluation have been completed on 2,6-xylenol.

Table 4: Xylenols Category Data

	Acute mam-malian toxicity	Repeat dose toxicity	Gene tox (point mutat)	Gene tox (chrom-osome)	Repro-tox	Devel-opment tox	Acute fish tox	Acute daphnia tox	Algal tox	Biodeg
2,5-xylenol	Rat oral 444 mg/kg	ND	Neg Ames	ND	ND	ND	EC50= 3-5 mg/L	EC50 10 mg/L	ND	ND
3,4-xylenol	Mouse oral 400 mg/kg	ND	Neg Ames	ND	ND	ND	EC50= 15mg/L	ND	ND	ND
2,4-xylenol	Rat oral 2300 mg/kg	3 Mo oral rat NOAEL 50 mg/ kg/day	Neg Ames	ND	ND	ND	EC50= 17mg/L	ND	ND	ND
3,5-xylenol	Rat oral 608 mg/kg	ND	ND	ND	ND	ND	EC50= 53mg/L	ND	ND	ND
2,3-xylenol	ND	ND	Neg Ames	ND	ND	ND	ND	EC50= 16mg/L	ND	ND
2,6-xylenol	Rat oral 296 mg/kg	8 Mo oral rat NOAEL 0.6mg/ kg/day	Neg Ames	Neg *In vivo*	ND	Rat Maternal NOAEL 60mg/kg Devel NOAEL 180mg/kg	EC50= 27mg/L	EC50= 11mg/L	IC50 range 325-460000 mg/L	Readily biode-gradable

ND = No Data

CATEGORY TEST PLAN

From inspection of Table 4, it can be seen that where complementary data exist on isomers, a concordance in results is apparent. Merisol notes that only a portion of the testing on 2,6-xylenol (some in mammalian cell *in vitro* mutation work, *in vivo* cytogenetics, and the developmental toxicity study) was conducted and reported under GLP conditions. Many details for the remainder of the work on xylenols are unavailable. Thus, while the existing mammalian

and ecological toxicology data, when viewed as a whole, strongly support toxicology data development on a xylenol 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 Mixed Xylenols Category. Merisol is not relying on data developed on analogous compounds to satisfy mixed xylenol testing but instead will develop data for each SIDS Screening Endpoint using the xylenol isomer mixture identified above and shown again below:

Mixed xylenols as a mixture containing equal portions of:

2,5-xylenol (CAS# 95874)
3,4-xylenol (CAS# 95658)
2,4-xylenol (CAS# 105679)
3,5-xylenol (CAS# 108689)
2,3-xylenol (CAS# 526750)
2,6-xylenol (CAS# 576261).

This mixture is intended to represent the Category "Mixed Xylenols" for HPV data development, as well as each separate xylenol isomer.

Data developed on this Category are intended to satisfy all requirements under the HPV Challenge Program for all mixtures of xylenols, as well as the individual xylenol isomers.

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

CONCLUSION

Xylenol 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 primarily to mixtures of xylenols, data developed on a mixture of six xylenols will provide cogent and reliable information for assessment of the potential hazards its xylenol-containing products may present to humans and the environment. This approach to data development also will account for any interactions between xylenol isomers that may impact toxicity, although none are expected.

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

Table 5: Mixed Xylenols 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.

Reduced SIDS Dossier: 2,6-Dimethylphenol, CAS Number 576-26-2, Sponsor Country USA, September 2, 1997.

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:

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