Interim Specific Ground Water Criterion
o, m, p-Cresol

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Introduction – Scope of this Assessment

The purpose of this assessment is to derive an interim-specific criterion ground water criterion for mixed cresols. It is, therefore, assumed that each of the three cresol isomers will be present at the site in question, but in an indeterminate proportion relative to each other. The criterion derived here will, therefore, be based on effects resulting from exposure to any of the isomers. As the isomers do not differ markedly either qualitatively or quantitatively in their toxicity this assumption appears reasonable.

USEPA derived RfDs and carcinogenicity assessments for the cresol isomers in the early 1990's in its IRIS database (although the RfD for p-cresol was subsequently withdrawn) (USEPA, 2010a, b, c). In this assessment, no attempt was made to review the full toxicological literature for cresols. Rather, the following strategy was followed. All relevant literature after 1990 (and thus unavailable at the time of the IRIS reviews) was searched. This included articles in peer-reviewed journals, the 2008 ATSDR Toxicological Review for Cresols (ATSDR, 2008), and reports from the National Toxicology Program (NTP). In addition, references used in setting the USEPA RfDs, and information submitted to the USEPA by manufacturers and their contractors under FIFRA and TSCA requirements were accessed. In addition, references cited by ATSDR that provided the lowest NOAELs and LOAELs identified by ATSDR were also identified regardless of their age.

Summary

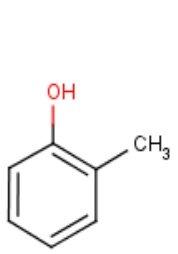
The cresols comprise a group of three closely related isomers, o-, m- and p-cresol. As environmental contaminants they are most commonly found as a mixture with varying proportions of these three isomers. This assessment is, therefore, intended to address total cresols and is, therefore, driven by the isomer yielding an adverse effect at the lowest dose for each toxicity category (systemic reproductive, etc.). The cresols all have similar physical properties with high water solubility and low vapor pressure. Cresols are well absorbed via the gastrointestinal tract, are rapidly distributed and excreted with a half-life on the order of hours. The USEPA designated cresols as a class C chemical with respect to carcinogenic potential (possible human carcinogen) under its the 1986 Guidelines for Carcinogen Risk Assessment. On the basis of more recent data and with respect to the USEPA's 2005 Guidelines, the corresponding designation of "suggestive evidence of carcinogenic potential" appears appropriate. Sub-chronic and chronic toxicity data identify a wide range of possible toxicities, but liver toxicity appears to be a common finding with a suggestion that low-dose increases in liver weight can progress to specific liver toxicity. Cresols have been observed to have reproductive toxicity, but these effects occur at higher doses than systemic chronic/sub-chronic endpoints.

Benchmark dose modeling was carried out for those data sets and endpoints for which appropriate data were available. The lowest BMDL derived from an appropriately fitting model was 21.9 mg/kg/day based on decreased hematocrit in female mice. This was identified as the point-of-departure (POD) for RfD development. Among the endpoints that were not amenable to benchmark dose modeling, the lowest NOAEL was 27

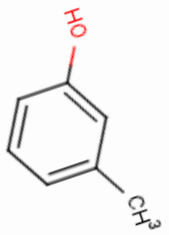
mg/kg/day based on increased relative live weight in female rats. An overall uncertainty factor adjustment of 300 was applied to the POD to yield an RfD of 0.073 mg/kg/day. Given the carcinogenicity characterization of "suggestive evidence of carcinogenic potential" and insufficient data to derive a cancer potency estimate, and additional uncertainty factor of 10 is applied to address potential cancer risk at the RfD. This yields an adjusted RfD of 7.3 x 10^{-3} mg/kg/day. The database is judged to be strong and the overall uncertainty in the RfD is judged to be moderate.

The Interim Specific Ground Water Criterion is derived by applying default exposure assumptions and the default relative source contribution factor and rounding to one significant figure to yield a value of 50 µg/L..

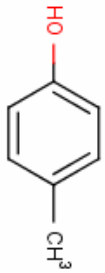
Physical and Chemical Properties



o-cresol



m-cresol



p-cresol

The three isomers of cresol have identical molecular weights (108.14 g/Mole). Their physical and chemical properties are similar but not identical. Table 1 presents selected parameters (ATSDR, 2008)

Table 1. Selected physical and chemical properties of cresols

	o-cresol	m-cresol	p-cresol
Water solubility (25°C)	25,950 ppm	22,700 ppm	21,520 ppm
Log octanol/water	1.95	1.96	1.94
Vapor Pressure (25°C)	0.299 mmHg	0.138 mmHg	0.11 mmHg

Given these properties, it can be assumed that, in general, the cresols will have significant water solubility, and will have a reasonable physical stability in dry soil with little potential for loss by volatilization.

Production, Use (ATSDR, 2008)

U.S. demand for cresols was projected to reach 385 million lbs annually in 2007. Cresols are used as solvents, disinfectants, and as intermediates in chemical manufacture, including pharmaceuticals, dyes, epoxides, pesticides, paints and textiles and as an additive to phenol-formaldehyde resins.

Pharmacokinetics and Metabolism (ATSDR, 2008)

p-Cresol occurs endogenously from the breakdown of the amino acids tyrosine and of phenylalanine. On the basis of systemic effects following high dose acute ingestion exposures to mixed cresols by humans, it appears that humans absorb a significant fraction of ingested cresols. On the basis of oral gavage studies on rabbits and rats, it appears that 65-100% of ingested cresols are absorbed systemically. Cresols appear to be rapidly distributed to various tissues from the blood. The highest concentrations were found in the liver and spleen with concentrations in brain, lung, and muscle similar to those in the blood. A portion of the ingested dose is conjugated as the glucuronide, and a smaller portion as the sulfate. The conjugates are the primary form of cresols excreted in the urine. Only a small fraction of the total dose is found unconjugated in the urine. Although there do not appear to be detailed information on the half-life of cresol in the human body, occupational data indicate that following exposure, the highest concentration of cresols in the urine are found 2 hours after the end of the work shift. This suggests that the elimination of cresol in humans is rapid. In rabbits, 65-84% of an ingested dose of cresols was eliminated in the urine in 24 hours.

Acute Toxicity (ATSDR, 2008)

In rats, cresols have an LD_{50} range of 100-250 mg/kg for single dose ingestion exposure to undiluted cresols and 1,000-2,000 mg/kg for single dose exposure to cresols diluted in olive oil. For a two week exposure, the LD_{50} in mice was reported as approximately 4,500 mg/kg/day. This relatively wide range suggests that at least some acute toxicity results from irritation/reactivity that is reduced when the same dose is less concentrated.

Carcinogenicity

USEPA-IRIS assessment of carcinogenicity

The USEPA's carcinogenicity assessment in IRIS is identical for each of the cresols (USEPA, 2010a, b, c). That assessment is based on two studies (Boutwell and Bosch, 1959). In both studies dermal application of cresol followed a single dermal application of dimethylbenzanthracene (DMBA), a known carcinogen. In the first study, 25 µl of

20% (v/v) o, m, or p-cresol in benzene was applied to mouse skin twice daily for 12 weeks. The mice experienced 29-52% mortality in the treated group compared to no observed mortality in the benzene control group. For o, m, and p-cresol, skin papillomas were observed in 59%, 50% and 35% of the mice respectively. The benzene-only control group experienced no mortality or papillomas.

In the second study, 25 μl of 5.7% (v/v) m or p-cresol in benzene was applied to mouse skin twice weekly for 20 weeks. There was decreased mortality at this dose (15-30% compared to 10% in controls). No papillomas were observed in the benzene vehicle control group. In the m- and p-cresol treated animals, skin papillomas were observed in 24% and 29% respectively.

USEPA also discussed short-term mutagenicity studies on cresol (unpublished data cited by USEPA in IRIS) including weakly positive results for unscheduled DNA synthesis in cultured human lung fibroblasts in the presence of liver homogenate with the o, m, p-cresol mixture and negative results for o-cresol alone; positive results for the BALB/3T3 mouse cell transformation assay with o, m, p-cresol mixture at non-cytotoxic doses and negative results for o-cresol alone; positive results for the o, m, p-cresol mixture in the mouse lymphoma cell culture forward mutation assay with liver homogenate and negative results for o-cresol alone with and without liver homogenate. Negative results were obtained in the Salmonella assay for o, m, and p-cresols with and without liver homogenate. Negative results were also obtained in the mouse fibroblast cell line C3H1OT1/2 transformation assay with p-cresol alone. In addition while no sister chromatid exchange was observed in Chinese hamster ovary cells for each of the cresols individually, sister chromatid exchange was observed when the cells were exposed to the o, m, p-cresol mixture.

On the basis of these observations, the USEPA designated cresols as a class C chemical – possible human carcinogen in 1991.

In light of the USEPA's subsequent 2005 Guidelines for Carcinogen Risk Assessment (USEPA, 2005), this designation, roughly corresponding to the 2005 category of "Suggestive Evidence of Carcinogenic Potential," appears to be problematic. This is because the Boutwell and Bosch (1959) mouse dermal application studies were essentially studies of the co-carcinogenicity of cresol in conjunction with DMBA. What was likely tested in these assays was the ability of cresols to promote the development of a tumor that had previously been initiated by DMBA. It is not clear how co-carcinogenicity fits into the structure of the hazard characterization scheme employed by the USEPA and NJDEP. More specifically, it is not clear whether it is appropriate to characterize a chemical that is not independently carcinogenic (i.e., in the absence of other chemical exposures) as a carcinogen *per se*. Even within the context of co-carcinogenicity, it is not clear to what extent these two-related studies examining the co-carcinogenicity of cresols in conjunction with only a single co-carcinogen (i.e., DMBA) can be extrapolated to a more generalizable co-carcinogenicity for cresols. Based on a search of the USEPA-IRIS database, there does not appear to be any other chemical for which co-carcinogenicity was the only in-vivo criterion supporting a classification of

carcinogenicity. Another problem with the use of these data is their use of benzene as a solvent for the cresols. While the benzene-only control mice did not develop skin papillomas, benzene is toxic by several different mechanisms and a possible role for benzene in the observed tumor promotion with cresol cannot be ruled out.

The positive results observed in some of the mammalian mutagenicity assays suggests that at least some, and possibly all, of the cresols have the ability to accomplish some of the steps required for tumor production. However, the lack of positive results in the Salmonella revertant assays suggests that cresols are not direct acting mutagens. Nonetheless, it is not clear that the positive results in these assays in conjunction with the co-carcinogenicity observed by Boutwell and Bosch (1959) are sufficient to warrant the characterization of cresols as providing "Suggestive Evidence of Carcinogenic Potential."

NTP (2008)

The National Toxicology Program conducted a 2-year cancer bioassay in male F344 rats, and female B6C3F1 mice 50/dose group with a 60/40 mixture of m- and p-cresol in the diet (NTP, 2008). The use of a single sex per species and restriction of the cresol isomers to the m- and p- forms was based on results of the subchronic NTP study using all cresol isomers (see below). Animals were evaluated with full pathology and histopathology. In addition, several short-term mutagenicity assays were conducted on this mixture.

Rats

Rats consumed food with concentrations of the cresol mixture of 1,500, 5,000, or 15,000 ppm. These gave corresponding time-weighted average doses of 70, 230, 720 mg/kg/day. High dose rats had an 18% decreased body weight compared to controls. This may indicate an exceedance of the maximum tolerated dose (MTD). However, food intake for these rats was also decreased suggesting that decreased body weight may have been related to palatability issues. At the next highest dose, there was a 5% decrease in body weight compared to controls.

Renal tubule adenomas (benign) were observed in 4/50 high dose animals. This incidence exceeded the NTP historical control values for this tumor (0.3-0.6% depending on the type of study included in the comparison and the specific method statistical characterization). However, the observed incidence was not statistically significant in the context of this study ($p = 0.054$). At other doses and in controls, adenomas were observed in 0/50 animals.

High dose animals had a statistically significant increase in eosinophilic hepatic foci (23/50 compared to 14/50 for controls). At intermediate doses, the incidence was equal to or less than the controls.

NTP considers the observed high-dose adenomas to be a "minimal increase." It is notable that the adenomas occurred in the absence of observed renal hyperplasia. It should also be noted that the observed increase of these tumors occurred in the dose group also may have been in excess of the maximum tolerated dose. NTP hypothesizes

that these neoplasms resulted from production of quinone-like metabolites as a minor metabolic product. The observed eosinophilic hepatic foci are generally considered to be a potentially pre-carcinogenic effect. However, liver tumors were not seen in this study.

Mice

Mice consumed food with concentrations of the cresol mixture of 1,000, 3,000, or 10,000 ppm. These gave corresponding time-weighted average doses of 100, 306, 1,042 mg/kg/day. Mice at the highest and second highest doses had a body weight 12% and 25% less than controls respectively. Both exposures may have exceeded the MTD. However, food intake was also decreased suggesting palatability issues may have been involved

Squamous cell papillomas (benign) of the forestomach were significantly increased in high-dose mice (10/50). These neoplasms were not observed in control mice. At the two other doses, the incidence was 1/50 (not statistically significantly elevated). Hyperplasia of forestomach epithelium was observed in 2/50 high-dose mice.

In liver, eosinophilic foci were statistically significantly increased at 10,000 ppm (24%), For controls and other doses, the following incidence was observed: 0 ppm 2%, 1,000 ppm, 0%; 3,000 ppm, 4%.

As with the observed eosinophilic foci in the rats, there was no significant dose-related increase in neoplasms in the liver and no evidence of progression of these foci to tumors.

Mutagenicity

The o, m, and p-cresol separately as well as the m, p-cresol mixture were negative in various *Salmonella* and *E. coli* short term mutagenicity assays. There was no evidence of micronuclei in mouse peripheral blood erythrocytes after 13 weeks of administration of o, or the m, p-cresol mixture to mice. While the negative results in the bacterial assays are consistent with earlier studies cited by the USEPA (see above), those results as well as the negative results micronucleus assay do not contradict the positive results in the mammalian assays: unscheduled DNA synthesis; forward mutation assay; and cell transformation assays cited by the USEPA.

Summary of carcinogenicity findings

Based on renal adenomas in rats, NTP characterizes evidence for carcinogenicity in rats as equivocal.

Based on papillomas in mouse forestomach (in the absence of evidence of cytotoxicity) NTP concludes that there is “some evidence” of carcinogenicity in mice.

Sanders et al. (2009)

Sanders et al (2009), is a re-presentation of the NTP (2008) chronic bioassay discussed above. The authors, with one exception, are from the NTP.

Kidney adenomas

The 4/50 observed kidney adenomas in the high-dose rats were "just outside the range of statistical significance" (i.e., $p = 0.054$) and exceeding historical controls. These adenomas were not associated with an increased incidence of kidney hyperplasia. However, there was a statistically significant increase in transitional pelvic epithelial hyperplasia. The authors note that F344/N rats spontaneously develop chronic progressive nephropathy and they hypothesize that this nephropathy increased susceptibility to cresol which, in turn, resulted in the observed increase in transitional renal pelvic epithelial hyperplasia and possibly adenomas. The absence of observed kidney adenomas in mice, is consistent with this hypothesis. Alternatively they hypothesize that exposure to cresol resulted in production of quinone-like compounds as minor intermediates leading to renal tubular damage primary to formation of adenomas.

Forestomach papillomas

With respect to the 20% incidence of (benign) forestomach squamous cell papillomas at the high-dose (10,000 ppm), the authors note that hyperplasia, with a severity of minimal-mild, was observed only at highest dose with an incidence of 4%. The authors note that irritative (nongenotoxic) chemicals can lead to tissue damage in the forestomach leading to regenerative proliferation and, ultimately, to tumors. However, they also note that there was only limited evidence of injury to gastric mucosa consistent with irritation. The authors also note that in the NTP sub-chronic 1992a study, there was evidence of regenerative changes in some animals in esophagus and forestomach (see below).

Summary of carcinogenicity findings

Sanders et al. (2009) concluded that "no clear evidence of carcinogenicity was observed in rats or mice." This conclusion is consistent with the conclusions of the NTP (2008) report *per se* that found that the evidence for carcinogenicity based on renal adenomas in rats to be equivocal and that there was some evidence of carcinogenicity in mice based on papillomas in mouse forestomach.

Carcinogenic potential of the cresols – summary and conclusions

The basis for the USEPA's classification of the carcinogenic potential of the cresols in its 1991 IRIS entry for each of the cresol isomers (i.e., promotion of skin tumors by dermal application following dermal application of a known cancer initiator) no longer appears entirely appropriate for consideration of a cancer potency via the ingestion route of exposure given the narrow and test system-specific nature of the evidence. While the short-term mutagenicity data presented by the USEPA in support of its determination is useful, the availability of the more recent and more route appropriate data from the NTP (2008) chronic bioassay provides a more appropriate and useful basis for assessing the carcinogenic potential of the cresols to humans through ingestion. There do not appear to be any other studies that provide direct evidence, either positive or negative, regarding the carcinogenic potential of the cresols.

The NTP (2008) study differs somewhat from the classic, full-scale NTP model in using only one sex per species. In addition, the NTP study was limited to a mixture of m and p-cresol (i.e., o-cresol was not addressed). However, findings from the earlier subchronic NTP (1992a) study as well as other studies of non-carcinogenic endpoints (see below) conducted on both sexes of rats and/or mice and using each of the cresol isomers or a mixture of all of the isomers strongly suggest that the NTP (2008) chronic bioassay design adequately represented the carcinogenic potential of both sexes and all isomers.

The direct evidence for carcinogenicity from the NTP (2008) study consists of kidney adenomas in rats and forestomach papillomas in mice. The kidney adenomas occurred only in the rats, only at the high dose, and only approached (but did not reach) statistical significance compared to controls. However, the high-dose adenomas incidence was clearly elevated compared to historic NTP controls for the F344 rat strain. Although Sanders et al (2009) hypothesize a relationship among the chronic endogenous neuropathy in F344 rats, the observed transitional renal pelvic epithelial hyperplasia, and the development of adenomas, this connection is speculative. Furthermore, the transitional renal pelvic epithelium and does not appear to have necessarily been spatially associated with the site of the adenomas. Sanders et al. (2009) alternatively propose that the adenomas could have resulted from the action of a minor quinine-like metabolite of cresol. Both pathways are plausible for susceptible human populations. In addition, it is noteworthy that the adenomas were not associated with surrounding hyperplasia as might have been expected if the adenomas were secondary to tissue injury followed by regeneration.

Because, unlike rodents, humans do not have a forestomach, there is a longstanding controversy regarding the relevance and interpretation of rodent forestomach tumors to humans. IARC (1999) has reviewed the etiology of rodent forestomach tumors to humans. Its assessment is that forestomach tumors can arise through both primary genotoxic mechanisms and from initial cytotoxicity and subsequent sustained cell proliferation and hyperplasia. Based on their negative results in bacterial mutation assays, cresols do not appear to be primary genotixic agents. However, the lack of consistent observed hyperplasia in conjunction with the observed mouse forestomach tumors does not clearly suggest a cytotoxic mechanisms resulting in regenerative hyperplasia.

It seems clear from the short-term assays cited by the USEPA (2010a,b,c) and conducted by the NTP (2008) that the cresols are not primary genotoxic chemicals. There does not appear to be any evidence indicating a direct interaction with DNA. However, the positive results in the sister chromatid exchange, inscheduled DNA synthesis, mouse lymphoma cell culture forward mutation, and mouse cell transformation assays suggests an epigenetic mode of action for tumor production. Such a mode of action might operate in the production of the forestomach tumors in the absence of primary cytotoxicity. Such a mechanism is potentially relevant to tumor production at other sites in humans.

Overall, the evidence for a carcinogenic potential for cresols that is applicable to humans is equivocal. Although there is evidence that the m-, p-cresol mixture produced tumors in two species of animals and in different sexes, the relevance of the observed tumors to humans and the appropriateness of extrapolating the high-dose-only tumors to much lower doses is uncertain. Nonetheless, there is no clear basis for judging either the kidney adenomas or the forestomach papillomas to be irrelevant to humans.

With respect to the USEPA's Guidance for Carcinogenic Risk Assessment (USEPA, 2005), the most appropriate descriptor for the cresols appears to be "suggestive evidence of carcinogenic potential." This descriptor includes chemicals for which there is "a small, and possibly not statistically significant, increase in tumor incidence observed in a single animal or human study that does not reach the weight of evidence for the descriptor "Likely to Be Carcinogenic to Humans," and chemicals for which there is "a statistically significant increase at one dose only, but no significant response at the other doses and no overall trend."

Chronic/Sub-Chronic Toxicity (Non-Cancer)

USEPA-IRIS assessment of non-cancer toxicity

The USEPA's IRIS data base gives RfDs for o- and m-cresol only. In both cases, the RfDs are based on a NOAEL of 50 mg/kg/day and a LOAEL of 150 mg/kg/day from studies conducted in 1986 and 1987 for the USEPA Office of Solid Waste. These appear to be identical to the studies reviewed and discussed below as USEPA 1988a,b,c and the TRL (1986). For both o- and m-cresol, USEPA identifies a NOAEL of 50 mg/kg/day and a LOAEL of 150 mg/kg/day based on decreased body weight and neurological effects. Both of these effects are likewise identified in this review (see below). However, as discussed below, it is unclear whether, on the basis of neurological effects presented in TRL (1986) 50 mg/kg/day is truly a NOAEL or a minimal LOAEL. The studies considered by USEPA are reasonably well conducted and appropriate for consideration for risk assessment. However, several studies have appeared subsequently that provide information not available at the time of the USEPA IRIS deliberations.

NTP (2008)

The only chronic study of the toxicity of the cresols is the 2-year bioassay with a 60/40 m,p-cresol mixture of male F344 rats and female B6C3F1 mice discussed above with respect to carcinogenicity (NTP, 2008).

Rats

As above, in addition to the unexposed control group, the rats were exposed to the m-,p-cresol mixture in their feed at concentrations 1,500 ppm, 5,000 ppm, 15,000 ppm, corresponding to time-weighted average doses of 70, 230, 720 mg/kg/day.

As discussed above, the 15,000 ppm group had an 18% decrease in body weight compared to controls by the end of the study. While this is a sufficiently large decrease in body weight to be considered an adverse effect, food intake for this group was also reduced. It is, therefore, not clear to what extent this resulted from palatability issues as opposed to a systemic effect of the cresol exposure.

As noted above, mild hyperplasia of the transitional epithelium of the renal pelvis was seen in the 15,000 ppm (720 mg/kg/day) group. Nephropathy was seen in controls and at all doses with no clear dose-response for incidence. NTP notes that nephropathy is known to be an age related occurrence in the strain of rats. However, the severity of the nephropathy increased at the two highest doses, from a severity rating of 1.4 in controls and low-dose rats, to 1.7 at the second highest dose, and 2.1 at the highest dose. Thus, cresols may exacerbate underlying age-related tubular degeneration.

At the highest dose, there was a significant increase in (microscopic) eosinophilic hepatic foci. While not a clearly defined adverse effect in itself, this is generally considered to indicate a cellular change that is a marker of carcinogenic potential. However, liver tumors were not observed in this study.

Angiectasis (distension or dilation of blood vessels) in the liver was significant at the highest dose with a possible indication of an effect at the second highest dose (0 mg/kg/day, 5/50; 70 mg/kg/day, 5/50; 230 mg/kg/day, 7/50; 720 mg/kg/day 14/50).

Hyperplasia of the nasal goblet cells and respiratory epithelium, metaplasia of the respiratory epithelium and nasal irritation were observed in the rats in a dose-dependent fashion. Hyperplasia was statistically significantly elevated above the control incidence at all doses. Metaplasia was statistically significant at the two highest doses. These lesions were observed primarily in the proximal portion of the nose (level I), only occasionally in the middle portion (level II), and not in the distal, olfactory region (level III). This suggests that these lesions were not systemic, but resulted from inhalation of vapor from and/or direct contact of the nose with cresol in the feed.

Mice

As above, in addition to the unexposed control group, the mice were exposed to the m,p-cresol mixture in their feed at concentrations of 1,000 ppm, 3,000 ppm, 10,000 ppm, corresponding to time-weighted average doses of 100, 306, and 1,042 mg/kg/day.

As above, body weight at the end of the study was 12% and 25% below that of controls for the two highest dose groups respectively. As with the rats, both decreases in body weight could indicate systemic effects. However, these decreases were also associated with decreases in feed consumption and so, may have been at least partly associated with palatability issues.

Thyroid follicular degeneration was significantly increased compared to controls at all exposures (0 ppm, 14%; 1,000 ppm, 50%; 3,000 ppm, 49%; 10,000 ppm, 42%). There

was no increase in severity with increasing dose. This may suggest that cresols can exacerbate an underlying, possibly age-related, thyroid effect.

Similar to the observation in the rats, there was a significant increase in hepatic eosinophilic foci at the highest dose. As with the rats, no liver tumors were observed in the mice.

Hyperplasia of the nasal epithelium was observed at the two highest doses and appears to have been confined to the proximal region (level I). This is consistent with the nasal effects observed in the rats. In contrast to the rats, however, the mice showed a significant increase in bronchiolar hyperplasia at all exposure groups (0 ppm, 0%; 1,000 ppm, 84%; 3,000 ppm, 90%; 10,000 ppm, 94%) with a increasing severity ranking with increasing dose (1.0, 2.0, 3.0 for 1,000, 3,000 and 10,000 ppm, respectively). The effect was most pronounced in the terminal bronchioles and extended to the alveoli. As with the respiratory effects in the rats, NTP suggested that these effects in the mice may have resulted from inhalation of cresol vapor from the food – especially during feeding. This appears likely at least for the nasal lesions. However, it is not entirely clear that this explanation can account for the lower respiratory effects given the lack of observed effects in nasal regions II and III. Alternatively, the lower respiratory effects may have been systemic.

Summary of NTP (2008) Non-Cancer Effects

In this study, the m,p-cresol mixture produced did not produce strong and clear-cut non-cancer endpoints. In rats, hyperplasia of the renal pelvic epithelium and angiectasis of the liver both occurred at a dose of 720 mg/kg/day. Significantly decreased body weight also occurred at this dose although it is not clear that this was due to systemic toxicity. The severity (but not the incidence) of nephropathy increased at the second highest dose (230 mg/kg/day). This appears to be an exacerbation of an underlying process rather than causation of the effect. In mice, a significant increase in the incidence of thyroid follicular degeneration was observed at the lowest dose (100 mg/kg/day). The relative high incidence of this effect in the control group (14%) suggests that action of cresol on the thyroid is to exacerbate rather than specifically to cause the underlying degeneration. Significant bronchiolar hyperplasia also occurred at the lowest dose (100 mg/kg/day), however, the significance of this lesion for environmental exposures is not clear.

Overall, this study produced an equivocal LOAEL of 100 mg/kg/day for exacerbation of thyroid follicular degeneration in mice. As this was the lowest administered dose, there is no NOAEL from this study.

NTP (1992a) - 28-Day Studies

The NTP conducted this 28-day study in conjunction with subsequent 13-week study. Both are reported together. In the 28-day study, 4-5-wk old F344/N rats, and 4 wk old B6C3F mice each sex were exposed to either o, m, or p-cresol, or to 60/40 m/p-cresol

mixture *ad libidum* in their feed. Each feed concentration group and for the controls consisted of 5 animals per species and sex, Both species were exposed to the same concentration in the feed - 0, 300, 1,000, 3,000, 10,000, 30,000 ppm.

Because the purpose of this document is to provide an assessment for mixed cresols of indeterminate proportions, the dose-related effects of any of the cresol isomers should be considered to apply to the mixture as a whole. Therefore, in the interest of clarity, the results from the NTP (1992a) study will be reported in the text based on the lowest appropriate concentration regardless of whether that concentration applied to o, m, p or m/p-cresol. In Tables 1-3, the individual isomer or mixture producing the referenced LOAEL/NOAEL and BMD/BMDL are identified.

Rats

At the highest dose, males and females had a statistically significant decrease in body weight compared to controls. The maximum decrease was 30% and 16% for males and females respectively.

Relative liver weight was significantly increased at doses ≥3,000 ppm for males and ≥1,000 ppm for females. Relative kidney weight was also significantly increased for males at doses ≥3,000 ppm and for females at ≥10,000 ppm. Significant increases in relative brain weight at the highest dose were judged by NTP to be secondary to decreased body weight rather than a primary effect of exposure.

Minimal-mild uterine atrophy (based on histopathology) was observed in 4/5 F at the highest dose. Minimal-mild femoral bone marrow depletion (decreased number hematopoietic cells) was observed at ≥ 3,000 ppm in males and at ≥10,000 ppm in females.

There was an increased occurrence of colloid in thyroid follicles accompanied by an increased follicle diameter, flattening of epithelial cells at ≥3,000 ppm in males and females. While the functional significance of this effect is not clear, it should be noted that this observation may be consistent with the follicular degeneration seen in the NTP (2008) study.

Minimal-to-mild hyperplasia and hyperkeratosis of the esophagus was observed at ≥ 3,000 ppm males and females. Minimal to mild hyperplasia and hyperkeratosis of the forestomach was observed at ≥10,000 ppm in females. Hyperplasia (without hyperkeratosis) was also observed for males at ≥10,000 ppm. Depending on the dose and sex, these effects were seen in 2/5-5/5 animals. This observation contrasts with the NTP (2008) chronic bioassay where papillomas of the forestomach were only sporadically associated with hyperplasia.

Consistent with the NTP (2008) chronic study, effects on the nasal epithelium were noted, but these were considered by NTP to be related to inhalation of cresol vapors from the food.

Mice
At the highest dose, up to 5/5 mice died during the course of the study. At the second highest dose, 1/5 mice died during the study. Mortality was associated with clinical signs indicating a causal effect of the dosing.

Body weight at the end of the dosing period was significantly reduced compared to controls at 30,000 ppm in females and at ≥10,000 ppm in males.

Relative liver weight was significantly increased for males at ≥1,000 ppm and for females at all doses (i.e., ≥300 ppm). Relative kidney weight was significantly increased for males and females at ≥3,000 ppm.

On histopathological examination, ovarian atrophy was observed at the high dose, uterine atrophy at ≥10,000 ppm, and bone marrow depletion in males and females at the high dose. As noted previously, nasal effects were seen and appear to be inhalation related.

Summary of 28-day study
For both rats and mice, the most sensitive effect was increased relative liver weight. For rats (females), this effect occurred with a LOAEL of 95 mg/kg/day and a NOAEL of 27 mg/kg/day. For mice (females), this occurred with a LOAEL of 66 mg/kg/day. As this corresponds to the lowest dose in this study, there was no NOAEL. Observations of associated liver lesions were largely absent. However, centrilobular liver necrosis was observed in high dose females (but not at the second highest dose). NTP suggested that this was treatment-related.

NTP (1992a) - 13-Week Studies

The doses in the 13-week study were chosen by NTP based on the findings in the 28-day study. The 13-week study was confined to either o-cresol, or a mixture of m/p-cresol. For rats, 20 animals were exposed per sex and dose to feed containing 0, 1,800, 3,750, 7,500, 15,000, or 30,000 ppm o, or m/p-cresol. Of these, 10 per sex and dose were used for analysis of clinical chemistry, hematology and urinalysis. The remaining 10 rats were used for assessment of reproductive toxicology, organ weight effects, pathology and histopathology. Thus, for each dose and each analysis/assessment, 10 animals of each sex were evaluated. For mice, 10 animals were exposed per sex and dose. The feed concentrations differed for o and m/p-cresol. For o-cresol, the concentrations were, 0, 1,250 , 2,500, 5,000, 10,000, and 20,000 ppm. For m/p-cresol, the concentrations were 0, 625, 1,250, 2,500, 5,000, or 10,000 ppm.

As was the case in the presentation of the results of the 28-day study, the results of the 13-week study will be reported as the lowest appropriate concentration regardless of whether that concentration applied to o-, or m/p-cresol.

Rats
Body weight at the end of the dosing period was significantly decreased compared to controls for males and females at ≥15,000 ppm.

Relative liver weight was significantly increased for males and females at ≥7,500 ppm. Relative kidney weight was significantly increased for males at 7,500 ppm and for females at ≥15,000 ppm. Relative testes weight was significantly increased for males at ≥15,000 ppm. Relative thymus weight was significantly increased for males at ≥15,000 ppm.

An increased incidence of minimal-to-mild bone marrow hypocellularity was observed for males at 30,000 ppm and for females at 15,000 ppm. NTP considers these effects likely to be secondary to decreased weight gain. However, it should be noted that in the 28-day study, minimal-mild femoral bone marrow depletion was observed at ≥ 3,000 ppm in males and at ≥10,000 ppm in females. NTP did not identify that, apparently related, effect as secondary.

There was a significant increase in bile acid concentration in the serum compared to controls in males at ≥3,750 ppm and for females at all doses. NTP attributes this affect to decreased hepatocellular function. However, this effect was seen inconsistently with respect to dose and with respect to the time course of the study and. For example, for females this effect was seen for 1,800 ppm of the m/p-cresol mixture on day 21, but not days 5, 43, or 90. At higher concentrations, however, this effect was seen on days 43 and 90. For males consuming the m/p-cresol mixture, this effect was seen for 3,750 ppm on day 90, but for 15,000 ppm on day 5, and only for 30,000 ppm on days 21, 43.

Mild-medium uterine atrophy was observed at ≥15,000 ppm. The length of the estrus cycle was significantly increased at ≥15,000 ppm**.**

As in the 28-day study and the NTP (2008) study, nasal effects were observed, but appear to be inhalation related (i.e., were mostly confined to anterior portion of the nasal cavity).

Mice

Body weight at the end of the dosing period was significantly decreased compared to controls for males at 10,000 ppm and for females at 5,000 ppm.

Relative liver weight was significantly increased relative to controls for males at all doses (i.e., ≥1,250 ppm) and for females at ≥5,000 ppm. Absolute (but not relative) kidney weight and relative thymus weight were significantly increased in females at 20,000 ppm.

Minimal forestomach epithelial hyperplasia was observed at 20,000 ppm in 40% of males and 30% of females and sporadically at lower doses. NTP suggests that this effect may have been do to irriation or secondary to reduced feed consumption.

As with the rats, nasal hyperplasia was observed in the anterior portions of the nasal cavity. The etiology of this effect appears to be similar in mice and rats.

Summary of 13-week study

The most consistent sensitive effect in both male and female rats appears to be increased relative liver weight with a NOAEL of 123 mg/kg/d and a LOAEL of 241 mg/kg/day. Increased liver weight was not associated with histopathological changes. Increased bile acid concentration in serum for females appears significant at all doses at some time points with a LOAEL of 131 mg/kg/day and no NOAEL. Males were also affected at some time points, but with a LOAEL of 241 mg/kg/day and a NOAEL of 123 mg/kg/day. This response was inconsistent over time and did not appear to be increase with time. It is therefore, not clear that this is a significant response with respect to long-term adverse effects. However, it does provide some indication that increased liver weight was associated with liver pathology. This suggestion is supported by the observation that the increased concentration of bile acids in serum occurred in a similar dose range to the liver weight effect. Thymus and tests weight changes have somewhat higher NOAELs as do uterine atrophy and lengthened estrus cycle. Overall, there is a suggestion of endocrine involvement.

Consistent with the observation in rats, the most sensitive effect in mice appears to be increased relative liver weight in males with a LOAEL of 199 mg/kg/day and no NOAEL. The corresponding NOAEL for females was 496 mg/kg/day. There was no indication of liver pathology in mice including no report of increased bile acids in serum.

Overall, the lowest NOAEL from this study was 123 mg/kg/day, and the lowest LOAEL was 199 mg/kg/day without a corresponding NOAEL.

Koizumi et al. (2003)

Koizumi et al (2003) exposed newborn (post-natal day 4-21) and young (5 wk old) Sprague-Dawley rats to p-cresol by gavage. Ostensibly, the purpose of the study was to compare the relative toxicity at these two life stages. However, the age range over which the newborn rats was dosed in this study roughly corresponds to the human periods of newborn-preterm infant to infant-toddler (Moser et al., 2005). Thus, the results from the newborn rats can serve to provide some information about the potential human developmental toxicity of cresol. Also, given the use of young animals, generally considered to be a sensitive sub-population, this study partly addresses uncertainty regarding sensitive individuals.

Newborn rats

Dose-finding study
Rats (5 per dose per sex) were exposed daily for 18-days by gavage on postnatal days 4-21 to 0, 100, 300, or 1000 mg/kg/day of p-cresol. Evaluations included general behavior, body weight, hematology, blood biochemistry, macroscopic pathology and organ weights.

All animals dosed at 1,000 mg/kg/day died within two days of the beginning of treatment.

At 300 mg/kg/day, all animals evinced deep respiration and tremors under contact stimulus. Females had a significantly decreased body weight at 300 mg/kg/day. No clinical signs were observed at 100 mg/kg/day.

Liver weight was significantly increased in males at ≥100 mg/kg/day and at 300 mg/kg/day in females. At 300 mg/kg/day males and females had a non-significant increase in blood bilirubin.

Main study
Doses in the main study were based on the results of the dose-finding study. Rats (12 per dose per sex) were exposed daily for 18-days by gavage on post-natal days 4-21 to 0, 30, 100, and 300 mg/kg/d p-cresol. Evaluation included general behavior, body weight, neurological signs, testes descent, vaginal opening, urinalysis, hematology, blood biochemistry, organ weights, histopathology of control and high dose organs (and organs at other doses with macroscopic changes or high dose changes in those organs).

Deep respiration and increased motor activity were seen at 300 mg/kg/day. Tremors upon contact stimulus were seen at 100 mg/kg/day in 3 of 12 animals, but only on a single day for each animal. Body weight was significantly decreased in males only at 300 mg/kg/day. Absolute brain weight was significantly decreased at 300 mg/kg/day in males and females. Relative liver weight was significantly increased in males and females at 300 mg/kg/day

Statistically significant increases in γGTP, bilirubin and BUN were seen at 300 mg/kg/day in males, but not in females.

No definitive changes in developmental parameters were observed at any dose including age at sexual maturation.

Young rats

Dose finding study
Five week old rats (5 per sex and dose) were exposed daily for 14 days by gavage to 0, 125, 250, 500, or 1,000 mg/kg/d.

No deaths occurred at any dose. Body weight was decreased in males at 1,000 mg/kg/day (it is not clear if this change was statistically significant compared to controls). Neurological effects (salivation, tremors, prone/lateral position) were observed at 1,000 mg/kg/day, but no clinical signs were observed at 500 mg/kg/day.

Relative liver weight was increased at ≥500 mg/kg/day (statistical significance not reported). Total cholesterol was increased in females at ≥500 mg/kg/day.

Main study
Five week old rats (7 per sex and dose) were exposed daily for 28 days

to 0, 100, 300, or 1,000 mg/kg/d. An additional 7 rats per sex were exposed at 1,000 mg/kg/day and maintained for 7 days after the end of the 28 day dosing period along with an additional 7 control rats.

No deaths occurred at any dose. Neurologic signs (salivation, tremor) were seen at 1,000 mg/kg/day for males and females. Body weight was significantly decreased at 1,000 mg/kg/day in males and females. No clinical effects were observed at 100 and 300 mg/kg/day.

Relative liver weight was significantly increased at ≥300 mg/kg day in females in females and at 1,000 mg/kg/day in males. Relative kidney weight was also significantly increased in females at 1,000 mg/kg/day.

Urine pH was decreased in males and females at 1,000 mg/kg/day. There was a significant decrease in GOT, and significant increases in cholesterol and BUN at 1,000 mg/kg/day in males. No biochemical changes were observed in females at any dose. No histopathological changes were observed in males or females at any dose.

Summary of Koizumi et al (2003)

Koizumi et al. concluded that newborn rats are approximately 3-4 times more sensitive to p-cresol than young rats. However, this assessment partially discounts the significance of the neurologic signs (esp. tremors) that were intermittently seen at a 10-fold lower dose in newborn rats. Liver weight increase gave a LOAEL of 100 mg/kg/d for newborn rats with no NOAEL and a LOAEL of 300 mg/kg/d with a NOAEL of 100 for young rats. Increased relative liver weight appears to be the most sensitive effect in this study. This is consistent with findings of liver weight increases in other studies. There is some biochemical evidence of liver pathology, but at doses greater than those producing increased liver weight (i.e., > 100 mg/kg/d for newborns and >300 mg/kg/d for young rats).

Hornshaw et al. (1996)

Hornshaw et al. (1996) described two related studies of o-cresol. The first study was a 28-day feeding study in European ferrets and mink. Although this study was described as an LC_{50} study, no mortality was reported at any of the doses. The second study was a reproductive study in mink only. In both of these studies the concentration of o-cresol in food was reported, but the reporting of body weights and feed consumption was incomplete and the dose (mg/kg/day) could not be reliably calculated from the data presented. The results are, therefore, summarized here relative to the feed concentration only.

28-day feeding study

Adult (approximately 6-months old) mink and ferrets (5 per sex and feed concentration) were given feed containing 0, 240, 432, 778, 1,400, 2,5200 ppm and 0, 432, 778, 1,400, 2,520, 4,536 ppm o-cresol respectively.

Mink experienced a statistically significant decrease in body weight at 2,520 ppm. There was a statistically significant decrease in erythrocyte count in mink at ≥1,400 ppm, and in ferrets at 4,536 ppm.

Relative liver weight was significantly increased in mink at all concentrations >240 ppm. For ferrets, a significant increase in liver weight was reported only relative to brain weight at all concentrations >778 ppm.

Reproductive study

Adult (approximately 9-months old), first year breeder mink were used in this study. There were 12 females per feed concentration (0, 100, 400, 1,600 ppm). Although there is some uncertainty in the reporting, it appears that there were 4 males per feed concentration and that each male was mated with 3 females within the feed concentration group. Exposure was begun 2 months prior to mating, and extended 6 wks post-partum (i.e., to weaning), giving a total of 6 months of exposure

Males consuming 1,600 ppm had a statistically significant decrease in body weight. There were no effects on reproductive performance. The only effect on body weight of kits was a statistically significant increase compared to controls for the maternal 100 ppm concentration. No birth defects were noted.

No lesions were noted in adults on necropsy. A significantly increased erythrocyte count (but not hemoglobin concentration or hematocrit) was observed at 1,600 ppm. This observation reflected the mean value for 4 males and 4 females. No significant differences were found in organ weights relative to brain weight. However, since body weights were not measured (due to concerns about handling during pregnancy) relative organ weights (including relative liver weight) were not reported.

Summary of Hornshaw et al. (1996)

The observed increase in relative liver weight is qualitatively consistent with other studies. Based on feed concentration, the NOAEL for this effect in mink was 240 ppm and the LOAEL was 432 ppm. Because of incomplete body weight and food consumption data reported in this paper, the corresponding doses cannot be calculated exactly. However, based on the limited data presented, there is an indication that this dose was roughly consistent with the LOAELs/NOAELS reported from other studies for rats and mice (i.e., <100 mg/kg/day). The changes reported in adult erythrocyte count in the 28-day and reproductive studies are contradictory. There is no obvious explanation for this. At these exposures o-cresol appeared to have no effect on reproductive performance or birth parameters.

NTP (1992b)/Izard et al. (1997)

The results of this study are presented as a technical report (1992b) and as an extended abstract (Izard et al., 1997). This was a two-generation reproductive study of a mixture of m/p-cresol in Swiss CD-1 mice. Aspects of developmental toxicity were also examined, but this was restricted to the F_1 generation. Of The F_0 generation (males and females, 20 pairs per dose group) were provided feed with 0, 2,500, 10,000 or 15,000 ppm of the mixture. Pairs continuously co-habited. These exposures were reported to correspond to doses of 0, 370, 1,500 and 2,100 mg/kg/day.

Some mortality (1-3 per dose group) was reported, but the highest incidence was in the control group and the cause of death was not determined.

There was no significant effect on the number of litters per pair, but the number of live pups per litter was reduced approximately 20% at the high dose. There was a 5% reduction in pup weight at birth (adjusted for litter size) at the highest dose. In addition there was in increase in the number of days to delivery at the high dose.

Pup viability was not affected by exposure at any dose. At weaning, (day 21) pup body weight was reduced compared to controls at all doses - 10, 28 and 23% at the low, mid and high doses respectively. The extent of body weight reduction increased during lactation with pups of low-dose mothers unaffected at post-natal day 7, but affected as noted above at weaning on day 21. Although postpartum maternal body weight was reduced by 20% at the high dose, there was no apparent reduction of body weight or other adverse effects in the low and mid-dose dams. Thus, the reduction in pup weight at these doses does not appear to be secondary to maternal toxicity.

Crossover mating of controls (males or females) and high dose (males or females) such that either the male or female was a high dose animal, resulted in no effects on any of the fertility or reproductive endpoints with the exception of pup body weight (from either of the mating combinations), which was reduced 6 and 8%.

In F_0 males, seminal vesicle weight was reduced 10% at the high dose, but no effect on sperm parameters was observed. No change in the estrus cycle was observed.

In the F_1 generation, there was no effect on fertility, but there was a 13% reduction in (litter size) adjusted pup weight in the F_2 generation.

In the F_1 males, absolute testes weight was reduced 10 and 8% at the mid and high dose, but there were no effects on sperm parameters. However male body weights were also reduced in the mid and high-dose groups by 10 and 8% respectively. Relative liver weight was significantly increased in males at the two highest doses and in females at all doses. Relative kidney weight was also increased in males at the highest dose and in females at all doses. There were no observed changes in the estrus cycle at any dose.

Summary of NTP (1992b)/ Izard et al.(1997)

The m/p-cresol mixture had an effect on pup body weight at maternal doses of ≥370 mg/kg/day. This does not appear to be related to maternal toxicity. In F_0 males, relative seminal vesicle weight was reduced at the high dose. Testes may have been affected in the F_1 generation by decreased weight at ≥1,500 ppm. This was reported on an absolute basis, since male body weight also decreased at these doses and no relative testes weight decrease was seen. Thus, the absolute decrease in testes weight may have been secondary to body weight effects. Overall, 370 mg/kg/day is a LOAEL for reproductive effects in this study. Despite an overlap in dose range, these results are not consistent with those reported by Hornshaw et al. (1996), who reported no effects on reproductive performance or kit status in their reproductive study in mink.

Tyl (1988)

This was a one-generation reproductive study with some developmental aspects also investigated. Female New Zealand whit rabbits (28 for controls, and 14 at each dose) were mated with single males and dosed once per day on gestational days 6-18 by gavage with o-, m- or p-cresol in corn oil at doses of 0, 5, 50, or 100 mg/kg/day and sacrificed on gestational day- 29. Gross examination of gravid uterus, ovaries, cervix, vagina, abdominal and thoracic organs and cavities was conducted. Live and dead fetuses were examined for gross malformations, visceral, skeletal and cranio-facial structures.

There was 14 and 36% maternal mortality (p-cresol only) at 50 and 100 mg/kg/day respectively. There were no apparent treatment related abortions. There were no significant differences in maternal weight compared to controls.

Maternal hypoactivity, abnormal breathing function (audible, rapid, labored, gasping), eye discharge, and neck swelling was observed at doses ≥50 mg/kg/day, Nasal discharge was observed at all doses (i.e., ≥5 mg/kg/day)

There were no apparent effects on reproductive or gestational parameters, or fetal viability and no dose related gross fetal malformations, visceral or skeletal variations. However, there was a statistically significant incidence of sub-epidermal hematoma on the head at 100 mg/kg/day.

Summary of Tyl (1988)

The maternal lethality observed at ≥50 mg/kg/day appears to be dose-related and not the result of gavage error. The effects on respiratory function and decreased activity at ≥50 mg/kg/day are consistent with similar observations from other studies. There is an apparent LOAEL at 5 mg/kg/day for nasal discharge with an incidence of 15, 27 and 56% and no occurrence in the controls. The report does not identify this as statistically significant, and the authors do not identify this as isomer-specific or a study-wide LOAEL. The reason for this is not clear. In common with many of the other effects, the dose related effect was observed during the dosing period, but not during the 10-day post

dosing observation. It may be appropriate to consider this a minimal acute-response effect.

The lack of effect on reproductive and viability parameters as well as on fetal formation within the dose range in this study is consistent with Hornshaw et al. (1996) and NTP (1992b)/ Izard et al.(1997) where effects were only observed at ≥370 mg/kg/day.

Tyl and Neeper-Bradley (1989)

This was a two-generation reproductive/developmental study of o-cresol (only) in rats. The F_0 generation was exposed pre-breeding through lactation. The F_1 generation was indirectly exposed via gestation and lactation, and then directly exposed from weaning through breeding and lactation. The F_2 generation was indirectly exposed (gestation and lactation) only.

Males and females (initially 25/sex/dose) were dosed by gavage with o-cresol in corn oil at doses of 0, 30, 175, 450 mg/kg/day. Dosing occurred over the course of approximately 30 days for males (through breeding) and approximately 51 days for females (through weaning). However, the exact timing is not clearly presented by the authors. Males were sacrificed following breeding and females were sacrificed following weaning.

In addition to visual (in-life) observation, animals were examined for gross lesions. Histopathological examination was carried out for controls and high dose animals and for animals at other doses with gross lesions. Histopathological analysis included pituitary, vagina, uterus, ovaries, testes, epididymides, seminal vesicles, and prostate and other tissue with gross abnormalities.

At 450 mg/kg/day, there was treatment related mortality in the F_0 and F_1 adult males and females with an incidence of 28-48%. No mortality was observed at other doses. Significantly decreased body weight in adults compared to controls occurred at ≥175 mg/kg/day in the F_0 generation and at 450 mg/kg/day in F_1 generation.

Clinical effects in adults (F_0 and F_1) included neurologic effects (ataxia, hypoactivity) at ≥175 mg/kg/day in the F_1 and at 450 mg/kg/day in the F_0. Two F_1 females were observed to be hypoactive on day 10. It is not clear that this is a clear LOAEL as hypoactivity at the two higher doses was observed throughout the 16 weeks of observation. Effects on respiratory function (audible/gasping/rapid respiration) occurred at 450 mg/kg/day with non-statistically significant low incidence and/or short-term/single day duration at all doses. Eye and nasal exudate/encrustation were observed at all doses (but not in controls), but with low, non-significant incidence.

For both the F_1 and F_2 generations, reproductive parameters (e.g., litter sizes, sex ratios, pup body weight, pup survival) were not affected by treatment at any dose.

Summary of Tyl and Neeper-Bradley (1989)

This study provides detailed two-generation reproductive toxicity information with some information on developmental effects in the F_1 generation. The lack of reproductive/developmental effects in the F_0, F_1, or F_2 generations is consistent with Hornshaw et al. and Tyl (1988), but somewhat inconsistent with NTP (1992b)/Izard et al. (1997) who reported pup body weight reductions at $\geq$370 mg/kg/day. This may reflect the fact that NTP (1992b)/Izard et al. (1997) used a mixture of m/p-cresol, while Tyl and Neeper-Bradley (1989) used only o-cresol. The difference in species between these studies (rabbits in NTP (1992b)/Izard et al. (1997), and rats in Ty and Neeper-Bradley (1989)) may also explain the apparent disparity in these studies.

The LOAEL in this study is 175 mg/kg/day for decreased body weight and neurologic effects. The neurologic effects at this dose were observed in the F_1 adults. Similar effects were seen in the F_0 generation, but at the next highest dose. This difference may reflect lactational exposure of the F_1 generation resulting in an overall larger total dose and longer duration of exposure. The NOAEL for this study is 30 mg/kg/day.

USEPA (1988a,b,c)
(Note: These studies have also been referred to in other citations as Diets and Mulligan, 1988)

USEPA. (1988a) – o-cresol
Sprague-Dawley rats (30 per sex and dose) were treated by gavage with o-cresol in corn oil once per day for 13-14 consecutive weeks at doses of 0, 50, 175, and 600 mg/kg/day.

Significant mortality was observed at 600 mg/kg/day, apparently due to transient CNS depression. Survivors recovered in 1 hr. Tremors were observed in 2 females at 175 mg/kg/day on single days.

There was a significant decrease in body weight relative to controls in males at 600 mg/kg/day during weeks 2-10, and at 175 mg/kg/day during wk 2 only. No body weight effects were observed for females.

There were no significant differences in organ weights compared to controls. Clinical chemistry, hematology, urinalysis parameters were not affected. No pathology was noted (other than lethality at 600 mg/kg/day) at any dose.

The tremors on isolated days appear consistent with sporadic tremors in newborns at 100 and 300 mg/kg/d observed by Koizumi et al. (2003).

USEPA (1988b) – p-cresol
Sprague-Dawley rats (30 per sex and dose) were treated by gavage with p-cresol in corn oil once per day for 13-14 consecutive weeks at doses of 0, 50, 175, and 600 mg/kg/day.

At 600 mg/kg/day, there was mortality in 3/30 rats. Tremors and convulsions observed in 2 of these 3 rats. This is consistent with observation in USEPA (1988a) of mortality resulting from transient CNS depression. Lethargy, salivation, and tremors with occasional convulsions and coma were observed in the surviving male and female rats dosed at 600 mg/kg/day. These effects were not seen at lower doses. No other clinical signs were seen at other doses.

Significantly decreased body weight compared to controls was seen in males at 600 mg/kg/day during the entire dosing period. Decreased body weight was also seen in males at 175 mg/kg/day, but only during the first 3 weeks of dosing. Significantly decreased body weight compared to controls was also observed in females at 600 mg/kg/d in females during 9 of the 13 weeks of dosing. A significant decrease in body weight compared to controls for females was also seen at 50/mg/kg/day, but only for 5 of the 13 weeks at the beginning of the dosing period.

A suite of possibly related liver effects were seen at 600 mg/kg/day: significant elevated of SGPT and SGOT (females); chronic hepatic inflammation in 2/18 (females); significantly elevated serum cholesterol (females) and a non-significant elevation at 175 mg/kg/day (males and females); and significantly increased relative liver weight with a non-significant increase at 175 mg/kg/day (males).

A significant decrease in erythrocyte count, hemoglobin concentration and hematocrit was seen in females (but not males) at ≥175 mg/kg/d. Total serum protein was significantly elevated at ≥175 mg/kg/day (males). Relative kidney weight (females) was also elevated at ≥175 mg/kg/day. Relative heart, testes and brain weights were significantly elevated at 600 mg/kg/d (males).

There was a significant increase in chronic nephropathy in males at 50 and 600 mg/kg/day (but not 175). Epithelial metaplasia of trachea was significant at 600 mg/kg/d. However, it is possible that this effect is related to the gavage route of exposure**.**

USEPA (1988c) – m-cresol

Sprague-Dawley rats (30 per sex and dose) were treated by gavage with m-cresol in corn oil once per day for 13-14 consecutive weeks at doses 0, 50, 150, and 450 mg/kg/day.

Lethargy, and sporadic tremors in males and females were seen at 450 mg/kg/day. Body weight was significantly decreased compared to controls at ≥150 mg/kg/day in males only. Unlike the case for the other cresol isomers, the decrease in body weight compared to controls for m-cresol was consistent with time after the third week.

No effects were seen for clinical chemistry, hematology, urinalysis. No significant effects were seen for organ weights. No gross or pathological lesions were observed.

Summary of USEPA (1988 a,b,c)

Taking these studies together, the most sensitive endpoint appears to be decreased body weight with a LOAEL of 150 mg/kg/day and a NOAEL of 50 mg/kg/day. Hematological

effects and relative kidney weight increase occurred with a LOAEL of 175 mg/kg/day and a NOAEL of 50 mg/kg/day. While liver effects were noted only at higher doses, it is notable that several of the liver effects indicate clear liver toxicity.

Kitigawa (2001)

This was an *in vitro* study of the effect of the cresol isomers on rat liver mitochondrial function.

Isolated rat liver mitochondria were o, m, or p-cresol along with glutamate or succinate. Over the range of 0.2-1.2 μmol/mg protein, all of the cresols reduced measures of mitochondrial respiration (state-3 respiration, RCR) by 20-80%. Each isomer induced mitochondrial swelling in the absence of Ca^{++} and accelerated mitochondrial swelling in the presence of Ca^{++}. The author suggests that mitochondria may be a target of cresol hepatotoxicity.

Summary of Kitagawa (2001)

This study suggests a mechanism for liver toxicity and suggests that effects on liver mitochondria could affect overall liver function and might explain some or all of the liver effects seen in the various *in vivo* studies.

TRL (1986)

This was a subchronic study of o, m and p-cresol separately that focused on neurological endpoints.

CD rats at 7-weeks of age (30 per sex and dose) ingested m-, p-, or o-cresol in corn oil by gavage once per day for 13 consecutive weeks. For o and p-cresol the doses were 0, 50, 175, 450, 600 mg/kg/day and for m-cresol the doses were 0, 50, 150, 450 mg/kg/d.

Elevated mortality occurred at the highest doses, but aspiration of cresol appears to have been a cause in at least some of these. There were no significant treatment-related body weight effects except for a transient (1-week) decrease at 600 mg/kg/day.

Sporadic salivation was observed at ≥50 mg/kg/day with a high incidence at ≥450 mg/kg/day. Myotonus (muscle rigidity/spasm) was observed at doses >150 mg/kg/day. The incidence of myotonus was high during the first day of dosing, decreased significantly during the second week and then increased gradually throughout the study. This suggest an adaptive response that gradually becomes overwhelmed. Tremors were generally not seen at 50 mg/kg/day, but one rat at 50 mg/kg/day did exhibit tremors during the 6^{th} week of dosing. Urine-wet abdomen was sporadically observed at 50 mg/kg/day. The incidence at 450 mg/kg/day peaked and was maintained at the 6^{th} week of dosing,

Hypoactivity and rapid respiration was observed sporadically at 50 mg/kg/day, increasing in frequency at higher doses after the second week of dosing. Rapid respiration followed the same pattern. Hyperactivity with unspecified "low, and sporadic" incidence were observed at 50 mg/kg/day. The authors consider this effect to be treatment-related and indicative of nervous system stimulation. Convulsion were observed throughout the study at ≥450 mg/kg/d. Impaired gait was observed sporadically at ≥450 mg/kg/day. It is notable that hyperactivity was observed in addition to hypoactivity.

Myoclonus (muscle twitches) and low body posture were both observed at the lowest dose (50 mg/kg/day) with the highest incidence (at high doses) on the first day of dosing, but these effects were no longer present by the end of the study and week-8 respectively.

Summary of TRL (1986)

Cresols produced a range of relatively frank neurologic responses whose incidence followed a dose-response relationship and some of which appear to increase in incidence over the duration of the study. Other neurologic responses disappeared over the course of the study. This appearance may reflect an adaptation. For several of the effects (salivation, urine wet abdomen, tremors, hyper-and hypoactivity), there were sporadic and low incidence responses at 50 mg/kg/day. Thus, it is unclear whether 50 mg/kg/day represents a true NOAEL or a minimal LOAEL.

Overall Summary of Chronic/Sub-Chronic Toxicity Non-Cancer Studies

The most consistent and robust adverse endpoint that emerges from these studies is increased relative liver weight. Table 1 presents the LOAELS and NOAELS for this endpoint.

Table 1 – LOAELs and NOAELs by study for increased relative liver weight

Study	Species	Cresol isomer	LOAEL	NOAEL	Route of administration	comment
NTP (1992a) 28-day study	rats (F)	m//p-mixture	95 mg/kg/day	27 mg/kg/day	feed	
	mice (F)	m	66 mg/kg/day	none	feed	LOAEL was lowest dose
NTP (1992a) 13-week study	rats (M and F)	o and m/p mixture	241 mg/kg/day	123 mg/kg/day	feed	
	mice (M)	o	199 mg/kg/day	none	feed	LOAEL was lowest dose
Koizumi et al. (2003) (post-natal days 4-21)	newborn rats (M)	m	100 mg/kg/day	none	gavage	LOAEL was lowest dose
	young rats (F)	m	300 mg/kg/day	100 mg/kg/day	gavage	
Hornshaw et al. (1996) (28 day study)	mink (sex not specified)	o	432 ppm	240 ppm	feed	Insufficient information provided to calculate exact dose. However, estimate dose is <100 mg/kg/day

The lowest LOAEL is 66 mg/kg/day in mice in the NTP (1992a) 28-day study. The lowest NOAEL is 27 mg/kg/day for rats in the same study. However, the range of values across studies is relatively narrow and indicates good consistency across studies. It should also be noted that the LOAELs and NOAELs from the gavage administration study of Koizumi et al. (2003) are comparable to the values from the other feed exposure studies. There was no evidence of liver pathology at these doses. However, at higher doses, several studies observed effects that are consistent with liver pathology (increased serum bile acids, centrilobular liver necrosis, increased blood bilirubin, increased serum γGTP, increased serum cholesterol, decreased and increased serum GOT, chronic hepatic inflammation. In addition, the study of Kitigawa (2001) suggests a possible mechanism for liver toxicity in the effect of cresols on hepatic mitochondrial energy production. Taken together, these studies suggest that increased relative liver weight is an early effect that can progress to frank liver toxicity.

Table 2 presents selected LOAELs and NOAELs for endpoints other than increased liver weight.

Table 2 – LOAELs and NOAELs for endpoints other than increased liver weight

Study	Species	Cresol isomer	Effect	LOAEL	NOAEL	Route of Admin-istration	comment
NTP (2008)	Mice (F)	m/p mixture	thyroid follicular degeneration	100 mg/kg/day	none	feed	LOAEL was lowest dose. Appears to be an exacerbation of an endogenous effect rather than a primary effect
NTP (1992a) 13-week study	Rats (F)	m/p mixture	increased serum bile acid concentration	131 mg/kg/day (females)	none	feed	LOAEL in females was lowest dose. The occurrence of this effect was inconsistent over time and did not appear to progress with dose.
Koizumi et al. (2003)	newborn rats (M)	m	tremors with contact stimulation	100 mg/kg/day	30 mg/kg/day	gavage	Effect was seen only on a single day during the 18-day study for each effected animal.
USEPA (1988a,b, c)	rats (M)	m	decreased body weight at wk 14	150 mg/kg/day	50 mg/kg/day	feed	
	rats (F)	p	hematological effects (incl. decreased hematocrit)	175 mg/kg/day	50 mg/kg/day	feed	
	rats (M)	p	increased relative kidney weight	175 mg/kg/day	50 mg/kg/day	feed	
TRL (1986)	rats (M and F)	o,m,p	neurological effects	50 mg/kg/day	None/ 50 mg/kg/day	gavage	Effects at 50 mg/kg/day were generally sporadic and low incidence. It is not clear whether 50 mg/kg/day represents a NOAEL or a minimal LOAEL
Tyl (1988)	rabbits (matern-al dosing)	p	lethality	50 mg/kg/day	5 mg/kg/day	gavage	Dosing during gestational days 6-18
Tyl and Neeper-Bradley (1989)	rats (M)	o	Body weight decrease	175 mg/kg/day	30 mg/kg/day	gavage	In F_0 generation
	rats (F)	o	neurological effects	175 mg/kg/day	30 mg/kg/day	gavage	In F_1generation. Hypoactivity was noted at 30 mg/kg/day in two animals on a single day. It appears that this

							reflects a sporadic event consistent with a minimal LOAEL.

The non-liver-related effects reflect a wide range of toxicities. Some are study-specific. There is no obvious underlying mechanism among these effects. Other effects were seen at higher doses, but are not included in this table. Nonetheless, the selected effects cluster within a fairly narrow range of doses.

Sporadic neurological effects (e.g., tremors, hypoactivity) were seen at 50 and 30 mg/kg/day in TRL (1986) and Tyl and Nepper-Bradley (1989) respectively. In general, these were seen in one or a few animals on isolated days and did not occur consistently throughout the study. There is some indication that these effects occurred over a short duration immediately following dosing. As such, these effects are not considered here as the basis for a LOAEL. However, they constitute a source of uncertainty and warrant additional caution.

Reproductive and Developmental Toxicity

Studies providing information on reproductive and developmental toxicity are reviewed in detail above in the context of their chronic/sub-chronic toxicity data. Briefly, in the NTP (1992a) study, mild-medium uterine atrophy was observed at ≥15,000 ppm. The length of the estrus cycle was significantly increased at ≥15,000 ppm**.** Hornshaw et al. (1996) found no reproductive effects in a one-generation reproductive study in mink with concentrations up to 1,600 ppm in feed (no dose could be calculated from the data presented). NTP (1992b)/Izard et al. (1997) reported on a two-generation reproductive study in mice. The number of live pups was reduced at a maternal dose of 2,100 mg/kg/day and pup weight was reduced at maternal doses ≥370 mg/kg/day. There was equivocal evidence of testes effects in the F_1 generation at ≥1,500 mg/kg/day, and F_0 seminal vesicle weight was reduced at 2,100 mg/kg/day. No clear reproductive or developmental effects were observed in either Tyl (1988) or Tyl and Neeper-Bradley (1989).

The newborn rat portion of the Koizumi et al. (2003) study provides information on post-natal developmental endpoints in the rat. This roughly corresponds to human periods of newborn-preterm infant to infant-toddler (Moser et al., 2005). Comparing LOAEs and NOAELs from the newborn portion of this study to those from the young rat portion of the study suggests that newborn rats are 3-10 times more sensitive than young rats. The effects seen in the newborn rats were qualitatively similar to those seen in the young rats and in adult rats in other studies.

In summary, there is a reasonably large database on reproductive toxicity with two, two-generation studies. Information on developmental effects is more limited, although the reproductive studies provided information on gestational development and Koizumi et al. (2003) provided information on post-natal mouse development. On the basis of the

available evidence, while cresols have adverse reproductive effects, the LOAELs for these effects appear to be above the LOAELs for non-reproductive effects. As expected, based on Koizumi et al. (2003) newborn mice appear to be up to 10 times more sensitive than older mice. The greater sensitivity of newborns appears to be with respect to the same type of toxicity seen in the young mice in that study.

Dose-Response Assessment

For the neoplasms observed in the rats (renal tubule adenomas) and mice (forestomach papillomas), the occurrence of these lesions with borderline statistical significance or significance respectively and only at the high dose, argues against deriving a cancer potency slope for extrapolating to much lower doses in humans.

Benchmark dose modeling

Dose response data was evaluated using benchmark dose modeling (USEPA BMD model 2.1.2) for endpoints that showed temporally consistent responses and LOAELs of < 200 mg/kg/day. Benchmark dose modeling can be thought of as a way of estimating an ideal NOAEL that is independent of the specific doses used in a given study. Some of the endpoints suitable for benchmark dose modeling are for continuous data (i.e., for data expressed as discrete numerical values, such as body weight, as opposed to dichotomous, yes/no, outcomes such as lethality). For continuous data, it is necessary to specify the type of benchmark response parameter that will be used to calculate the benchmark dose (BMD) and the lower confidence limit on the benchmark dose (BMDL). The benchmark response (BMR) is the level of response that considered marginally adverse. For the case of body weight, it is the change in body weight relative to the control body weight that can be considered significant, especially if the body weight continues to change at correspondingly larger doses. Although there are several ways to choose such a response, a common parameter is a change of one standard deviation from the mean control value. This is the BMR parameter used in these calculations.

In contrast, the neurologic endpoints suitable for benchmark dose modeling are dichotomous data. For dichotomous data, the benchmark response (BMR) is defined somewhat differently from the BMR for continuous data. For dichotomous data the BMR is taken as a response that is close to (but necessarily within) the lowest observable response in data. With animal data generated from standard size studies, this level of response is generally about 10%. This value was used here as the BMR

Table 3 presents the BMD and BMDL values along with measures of the fit of the model to the observed data (AIC statistic and chi-square p-value) for selected models that give at least marginally acceptable fits. Note that where different models gave similar BMDL values, only results from representative models are shown. In each case, however, the results from the model giving the lowest BMDL are shown.

Table 3 – Benchmark Dose data for selected endpoints

Endpoint	Study	Benchmark dose model	BMD	BMDL	Fit statistic	Chi-square p-value
Decreased henatocrit in female rats	**USEPA (1988b) p-cresol – 13 wk study**	Continuous response- 2nd degree polynomial	91.5 mg/kg/day	58.9 mg/kg/day	102.6 (AIC)	0.30
		Continuous response- Power (power not restricted to ≥1)	29.9 mg/kg/day	0.2 mg/kg/day	102.0 (AIC)	0.48
		Continuous response- Exponential	55.4 mg/kg/day	21.9 mg/kg/day	101.7 (AIC)	0.71
Decreased body weight in male rats	**USEPA (1988c) m-cresol – 13 wk study**	Continuous response- 2nd degree polynomial	131.9 mg/kg/day	80.4 mg/kg/day	697.4 (AIC)	0.18
		Continuous response- Exponential	142.6 mg/kg/day	72.7 mg/kg/day	697.9 (AIC)	0.13
Increased relative kidney weight in male rates	**USEPA (1988b) p-cresol – 13 wk study**	Continuous response- Hill	163.3 mg/kg/day	61.3 mg/kg/day	-449.2 (AIC)	0.55
		Continuous response- 2nd degree polynomial	184.8 mg/kg/day	107.1 mg/kg/day	-448.8 (AIC)	0.38
		Continuous response- linear	392.2 mg/kg/day	294.3 mg/kg/day	-448.0 (AIC)	0.17
		Continuous response- exponential	173.3 mg/kg/day	77.8 mg/kg/day	-449.0 (AIC)	0.46
Ataxia	Tyl and Neeper-Bradley (1989) – 2 generation reprod. Study (F_1 F)	Dichotomous response- gamma	123.6 mg/kg/day	80.8 mg/kg/day	0.01 (chi sq)	0.997
		Dichotomous response- logisitic	127.3 mg/kg/day	93.9 mg/kg/day	1.6 (chi sq)	0.5
		Dichotomous response- Weibull	112.5 mg/kg/day	72.3 mg/kg/day	0.12	0.9
Hypoactivity [a]	Tyl and Neeper-Bradley (1989) – 2 generation	Dichotomous response- gamma	102.4 mg/kg/day	58.7 mg/kg/day	0.13 (chi-sq)	0.94

	reprod. Study (F_1 F)					
		Dichotomous response-log-logistic	109.0 mg/kg/day	66.9 mg/kg/day	0.07 (chi-sq)	0.97
		Dichotomous response-multi-stage	97.9 mg/kg/day	51.7 mg/kg/day	0.43 (chi-sq)	0.93
		Dichotomous response-quantal-linear	33.4 mg/kg/day	24.6 mg/kg/day	5.62 (chi-sq)	0.13
Hypoactivity [b]	TRL (1986) – 13 week study M	Dichotomous response - gamma	374.6 mg/kg/day	151.4 mg/kg/day	0.19 (chi-sq)	0.91
		Dichotomous response – quantal linear	410.2 mg/kg/day	286.8 mg/kg/day	0.05 (chi-sq)	0.99
		Dichotomous response – probit	224.3 mg/kg/day	110.8 mg/kg/day	1.87 (chi-sq)	0.76
	TRL (1986) – 13 week study F	Dichotomous response - gamma	361.1 mg/kg/day	146.6 mg/kg/day	0.20 (chi-sq)	0.90
		Dichotomous response - log-logistic	373.3 mg/kg/day	142.3 mg/kg/day	0.17 (chi-sq)	0.92
		Dichotomous response - log-probit	349.2 mg/kg/day	131.0 mg/kg/day	0.27 (chi-sq)	0.87
Rapid Respiration [b]	TRL (1986) – 13 week study M	Dichotomous response - gamma	445.8 mg/kg/day	188.2 mg/kg/day	0.10 (chi-sq)	0.95
		Dichotomous response - log-logistic	448.2 mg/kg/day	151.9 mg/kg/day	0.10 (chi-sq)	0.95
		Dichotomous response - log-probit	439.3 mg/kg/day	147.2 mg/kg/day	0.11 (chi-sq)	0.95
	TRL (1986) – 13 week study F	Dichotomous response - gamma	275.4 mg/kg/day	109.9 mg/kg/day	0.17 (chi-sq)	0.92
		Dichotomous response - log-logistic	278.9 mg/kg/day	99.4 mg/kg/day	0.16 (chi-sq)	0.92
		Dichotomous response - log-probit	291.1 mg/kg/day	55.2 mg/kg/day	0.22 (chi-sq)	0.89
		Dichotomous response - Weibul (power not restricted)	280.5 mg/kg/day	56.8 mg/kg/day	0.14 (chi-sq)	0.93

a. The benchmark dose modeling for this endpoint does not include the sporadic occurrence of hypoactivity in 2 animals on a single day at 30 mg/kg/day. For the purposes of this modeling, the incidence at that dose is taken to be 0.

b. Calculated based on the average daily (91 day) incidence using the highest daily incidence from either AM and PM observations and average number of animals per dose over the entire study duration.

For the data that were amenable to benchmark dose modeling, the endpoint giving the lowest BMDLs of 21.9 mg/kg/day, and 0.2 mg/kg/day (and lowest BMDs) is decreased hematocrit in female mice in the USEPA (1988b) 13-week study of p-cresol. The BMDL value of 0.2 mg/kg/day based on the unrestricted power model is more than two orders of magnitude less than the BMDL derived from the other models giving acceptable fits for this endpoint. The BMDLs derived from the two other models giving acceptable fits to these data (2^{nd} degree polynomial, exponential) differ by less than a factor of three. While the value of BMDL is not directly dependent on the study-specific NOAEL, it is instructive to note that the unrestricted power model BMDL giving the low value of 0.2 mg/kg/day, is also more than two orders of magnitude less than the corresponding NOAEL (Table 2). Figure 1a-c shows the fit of these models to the data and the resulting BMD/BMDLs.

As shown in Table 3, the fit of these models is roughly comparable. However, examination of Figure 1 shows that the neither the unrestricted power model, nor the 2^{nd} degree polynomial model provides a parsimonious fit to these data. In the case of the 2^{nd} degree polynomial model, the dip in the response function between the two highest doses is not theoretically necessary and is unlikely to be consistent with the true dose response. In the case of the unrestricted power mode, the precipitous decrease in the response function between the control value and the lowest dose is, likewise, theoretically unnecessary and unlikely to be consistent with the true dose response. It is this feature that is largely responsible for the low BMDL and BMD values from this model. In contrast, the exponential model provides a more parsimonious fit to the data in that it does not produce abrupt or theoretically doubtful features. Although the 2^{nd} degree polynomial model does not provide a parsimonious fit in the high dose region, its fit in the low dose region is theoretically reasonable. This is consistent with the relative similarity of the BMDL for this model with that from the exponential model.

In general, selection of a BMDL for a given endpoint is based on the selection of the lowest value from among those that provide an acceptable fit to the data. In this case, the BMDL from the unrestricted power model is not selected because of its unusual fit of the data and the resulting disproportionally small BMDL. Instead, the next smallest BMDL, derived from the exponential model, is chosen as the appropriate estimate. That value is 21.9 mg/kg/day.

It should also be noted that the hypoactivity endpoint from Tyl and Neeper-Bradly (1989) gave a BMDL of 24.6 mg/kg/day based on the quantal-linear model (dichotomous response). This value is only slightly larger than the BMDL derived for reduced hematocrit. However, the fit of that model to the data is relatively poor compared to the fit of the other models for this endpoint shown in Table 3 (other models gave similar fits to those shown in Table 3). Thus, this BMDL is considered less robust. It should also be noted that the lowest BMDLs generated from the TRL (1986) data for rapid respiration in

female rats (a neurologic endpoint) are about twice the value for the Tyl and Neeper-Bradley neurologic endpoint of hypoactivity.

Comparison of BMDLs and NOAELs

While Table 3 presents the BMDLs for each of the endpoints that were amenable to benchmark dose modeling, there were several endpoints for which none of the available dose-response models in the USEPA-BMDS software provided an adequate fit. The NOAELs for each of these endpoints is larger than the BMDL of 21.9 mg/kg/day derived above for decreased hematocrit in female rats in the USEPA (1988b) subchronic (13-week) study of p-cresol. The lowest NOAEL among the non-benchmark modeled endpoints was 27 mg/kg/day for increased relative live weight in female rats in the NTP 1992a study. Several other NOAELs were 50 mg/kg/day. As noted, the BMDL is not constrained by the study-specific NOAEL. Therefore, in theory, a BMDL derived from one of these studies might have a value less than a corresponding NOAEL and less than 21.9 mg/kg/day. Of particular note in this respect is thyroid follicular degeneration in mice in the NTP (2008) chronic bioassay. The maximum response for this effect was reached at the lowest dose (100 mg/kg/day). Because cresol appears to exacerbate this endogenous degenerative process, the no-effect dose for exacerbation of this process may be quite low. However, in the absence of BMDLs for this and other endpoints studies, there is no way to address this uncertainty.

Selection of a point of departure (POD)

The BMDL of 21.9 for decreased hematocrit derived from female rats in the USEPA (1988b) 13-week study of p-cresol is the lowest of the BMDL values that were derived from appropriately fitting models by benchmark dose modeling. It is the also smaller than any of the NOAELs for endpoints that were not suitable for benchmark dose modeling. The 13-week NTP (1992a) study also examined hematological endpoints, including hematocrit, in rats and mice. In that study, significantly decreased hematocrit was observed sporadically, but was not consistent with identification as a clear treatment related effect. Given the comparable dose ranges in the two studies, the reason for this discrepancy is not clear. The two studies used different strains of rats (F344 in the NTP (1992a) study, and Sprague-Dawley rats in the USEPA (1988b) study) and differences in strain sensitivity could potentially explain the difference in the occurrence of this endpoint. This apparent discrepancy notwithstanding, the effect seen in the USEPA (1988b) appear robust and describe a clear dose response relationship.

Therefore, given the available data and analyses, the point of departure (POD) for non-cancer endpoints is identified as 21.9 mg/kg/day for decreased hematocrit in female rats in the USEPA (1988b) 13-week study of p-cresol.

Risk Characterization

Uncertainty factor (UF) adjustments

The POD represents the highest dose determined to have minimal adverse effect (in this case, the lowest appropriate BMDL) for the available adverse endpoints in an animal model. As such, the POD is not specific to sensitive humans and not necessarily inclusive of all potential adverse endpoints. Therefore, in order to apply the animal data to an RfD that is appropriate for public health protection, it is necessary to address the uncertainties inherent in the difference between the POD and the dose protective to the sensitive human population.

Animal to human (interspecies) adjustment

Since it is unknown whether, and to what extent, the average human may be more sensitive to cresols than the rat that is the basis for the POD, a factor of 10 is applied ($UF_{interspecies} = 10$).

Average human to sensitive human (intraspecies) adjustment

It is assumed that sub-populations may be more sensitive than the average population. Potentially, these include children; the elderly; and those with underlying adverse genetic, disease, or nutritional factors. To address the potential differences in cresol sensitivity between these sub-populations and the average population, a factor of 10 is applied ($UF_{intraspecies} = 10$).

Subchronic to chronic exposure adjustment

Effective doses for a given endpoint are often lower with chronic exposures than with shorter exposures due to the potential for progression of low-level injury over the time frame that can be observed in chronic, but not subchronic studies. The POD is based on decreased hematocrit observed in a 13 week (i.e., subchronic) study in rats exposed to p-cresol. Although the database for cresols does include a high quality chronic study (NTP, 2008), that study did not examine hematological endpoints. On the other hand, the non-cancer endpoints identified in the NTP (2008) chronic bioassay have NOAELs that are larger than the POD identified from the subchronic USEPA (1988b) study. Therefore, given the quality and breadth of the NTP (2008) study it does not seem likely that other (non-hematologic) endpoints identified in the subchronic studies would produce chronic endpoints yielding lower PODs than those already identified in the NTP (2008) study. Therefore an uncertainty factor of 3 is applied to address limited subchronic to chronic adjustements in hematologic endpoints ($UF_{subchronic\text{-}chronic} = 3$).

Database insufficiency adjustment

The database for cresol toxicology is relative large. It contains a well conducted chronic bioassay, several well conducted subchronic and sub-acute studies, including one that specifically focused on neurological endpoints, as well as three reproductive studies, two of which were two-generational studies (NTP (1992b)/Izard et al. (1997; Tyl and Neeper-Bradly, 1989) and a study of effects in newborns that addresses some aspects of developmental toxicity. Although there was no study that specifically focused on developmental endpoints, the reproductive studies appear to have addressed all of the basic developmental test criteria. However, in light of the several neurological effects noted in adults, it would be preferable to have a study that focused on developmental

neurological endpoints. Overall, however, there do not appear to be any major database insufficiencies ($UF_{database} = 0$).

Reference Dose (RfD) derivation

The RfD is derived as the quotient of the POD and the product of the UFs:

POD/ ($UF_{interspecies}$ x $UF_{intrapsecies}$ x $UF_{subchronic\text{-}chronic}$) = 21.9 mg/kg/day/ (10 x 10 x 3) = 0.073 mg/kg/day.

Comparison to USEPA-IRIS RfD

The current USEPA-IRIS RfDs for o- and m-cresol is 0.05 mg/kg/day based on a NOAEL of 50 and a total UF of 1,000. The total UF is based on $UF_{interspecies}$ (10) x $UF_{intrapsecies}$ (10) x $UF_{subchronic\text{-}chronic}$ (10). There is currently no RfD for p-cresol. The value derived here differs from the USEPA-IRIS value in starting with a smaller POD (21.9 mg/kg/day versus 50 mg/kg/day) and in applying a smaller total UF (300 versus 1,000). The difference in the POD is based on the use of benchmark dose modeling, and the difference in the total UF is based on the availability of the NTP (2008) chronic bioassay.

Adjustment of RfD for cancer risk

As discussed in detail above, the cresols are judged to meet the carcinogenic characterization criterion of suggestive evidence of carcinogenic potential as described in the USEPA Guidelines for Carcinogen Risk Assessment (USEPA, 2005). It is also judged that there are insufficient data to derive a cancer slope factor (cancer potency estimate) for cresols. Therefore, the procedure, based on NJDEP policy, is to apply an additional UF to the RfD to address potential cancer risk at the exposure corresponding to the RfD. This yields an adjusted RfD of 0.073 mg/kg/day/10 = 7.3 x 10^{-3} mg/kg/day.

Characterization of uncertainty

The overall database for cresols is relatively large incorporating sub-chronic and chronic studies, as well as reproductive studies and studies that supply some developmental data. The database contains studies from both sexes of mice and rats as well as some studies in other mammals. Among the studies are comprehensive state-of-the-art chronic bioassays conducted by the National Toxicology Program (NTP) that address carcinogenic as well as chronic endpoints. There are no major insufficiencies in the database. The dose-response data are well represented at the lower and of the dose-response spectrum and much of the low-dose data gave robust fits in benchmark dose modeling. The database lacks useful epidemiologic studies, however, and the cancer data are largely equivocal. Uncertainty is introduced by the choice of data from an NTP subchronic data as the basis for the RfD. This required the application of an uncertainty factor to account for potential difference between the subchronic BMDL and a corresponding (but theoretical) chronic BMDL for the same endpoint. Additional uncertainty derives from the

application of an additional uncertainty factor to account for possible carcinogenicity at the RfD. Overall the database is judged to be strong and the overall RfD is judged to have moderate uncertainty.

Derivation of the Interim-Specific Ground Water Criterion

Application of NJDEP default interim-specific ground water assumptions

The default NJDEP assumptions for derivation of interim ground water criteria (ISGC) are:

Intake (I) - 2 L/day
Body weight (bw) – 70 kg
Relative source contribution (RSC) – 0.2

The ISGC is calculated as:

ISGC = [(RfD x bw)/I] x 0.2.

For the RfD_{adj} of 7.3×10^{-3} mg/kg-bw/day derived here the ISGC is given as:

ISGC = [(7.3×10^{-3} mg/kg-bw/day x 70kg-bw)/2 L/day] x 0.2 = 5.1×10^{-2} mg/L = 51.1 μg/L. Rounding to one significant figure gives a value of 50 μg/L.

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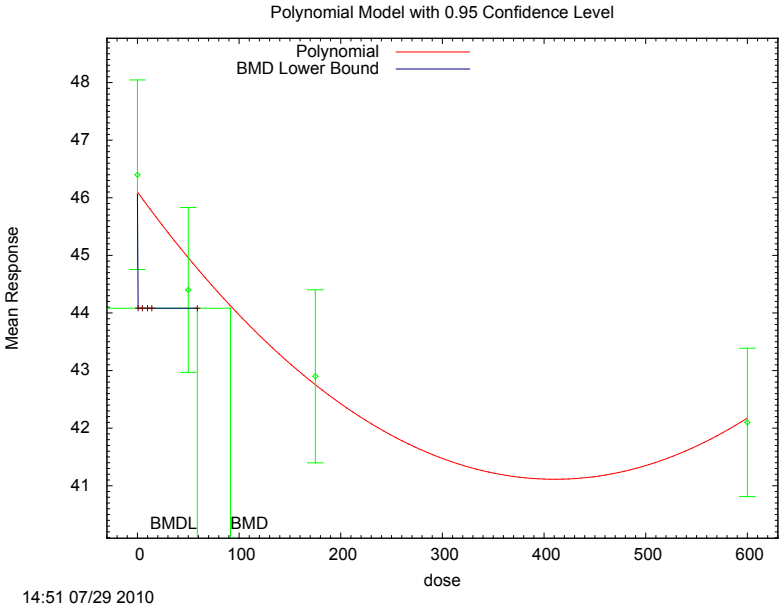
USEPA (2010). Integrated Risk Information System (IRIS), 4-methylphenol. Accessed at: http://www.epa.gov/ncea/iris/subst/0302.htm, 7/6/10.

Figure 1

a. Decreased hematocrit F rats – p-cresol, 13 week study USEPA (1998b)

2nd Polynomial model



b. Decreased hematocrit F rats – p-cresol, 13 week study USEPA (1998b)

Power model (unrestricted)

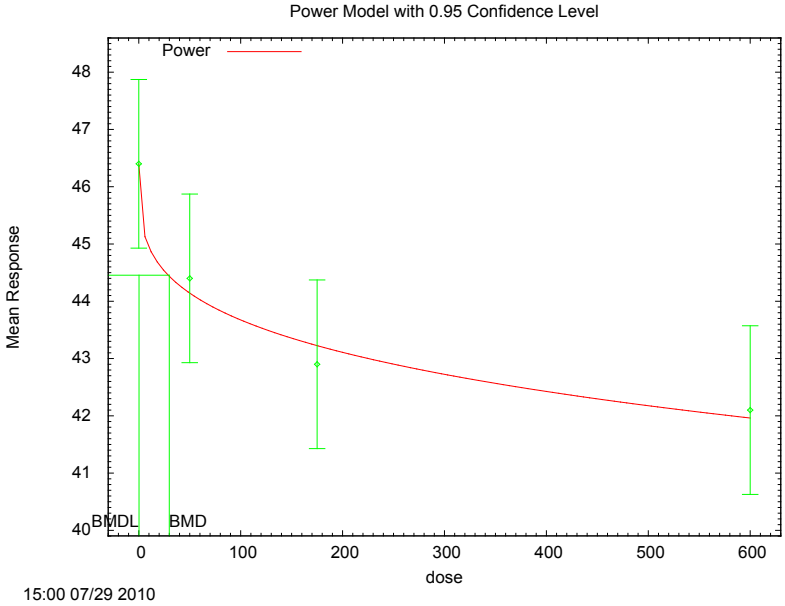


Figure 1 (cont'd)

c. Decreased hematocrit F rats – p-cresol, 13 week study USEPA (1998b) Exponential model