2. RELEVANCE TO PUBLIC HEALTH

2.1 BACKGROUND AND ENVIRONMENTAL EXPOSURES TO CRESOLS IN THE UNITED STATES

Cresols are widely distributed in the environment and the general population may be exposed to low levels of cresols mainly through the inhalation of contaminated air. Cresols are readily degraded in the atmosphere; atmospheric concentrations outside of source-dominated areas are typically low. Since cresols are released via automobile exhaust, areas of high traffic and gas stations are likely to have increased atmospheric levels of cresols. Cresols are also the product of combustion of coal, wood, and municipal solid waste; therefore, residents near coal and petroleum fueled facilities, as well as residents near municipal waste incinerators, may have increased exposure to cresols. There are limited air monitoring data for cresols; a median concentration of 1.5 μg/m^3 *o*-cresol was detected in air samples from 3 locations, the range of *p*-cresol at 11 locations was 0.5–20 μg/m^3, and *m*-cresol was not detected in air samples from 2 locations. A national emissions study conducted from 1990 to 1998 reported a county-level estimated ambient average concentration of 31.7 ng/m^3 for all cresol isomers combined.

Cresol levels in soil and water are usually low. When detected in surface water, cresol levels are typically around 1 μg/L or less. Higher levels are occasionally observed in groundwater or surface water where petroleum spills have occurred or near hazardous waste sites. In a study of public groundwater at superfund sites, *o*-cresol and *p*-cresol were detected at maximum concentrations of 390 and 150 μg/L, respectively; however, neither was detected in well fields or finished water from treatment plants (no data were provided for *m*-cresol). Due to their relatively rapid rate of biodegradation, cresols are only occasionally detected in soils, primarily in areas where petroleum products were spilled or produced. *o*-Cresol was detected at maximum concentrations of 12,000–34,000 μg/kg in soil samples obtained from an abandoned pine tar manufacturing plant in Gainesville, Florida.

Employees in occupations that routinely involve the combustion of coal or wood may be exposed to higher levels of cresols than the general population. Environmental tobacco smoke is also a source of cresol exposure. Depending on the brand and type of cigarette, the average cresol concentration in a 45 cubic meter chamber after six cigarettes had been smoked ranged from 0.17 to 3.9 μg/m^3.

Although low levels of cresol have been detected in certain foods and tap water, these do not constitute major sources of exposure for most people. Cresols have been reported in tea leaves, tomatoes, and ketchup as well as butter, oil, and various cheeses, but levels are not available. People with contaminated tap water can be exposed from drinking the water or eating foods prepared with it. In addition, inhalation can occur from volatilized cresol during showering, bathing, and cooking activities with contaminated water. Dermal exposure to cresols may also occur due to bathing or showering with contaminated water.

Exposure to children occurs by the same routes that affect adults. There are no known specific sources of exposure to children. Cresol has not been reported in breast milk or baby foods. Children are likely to be exposed to cresols through inhalation of contaminated air from automobile exhaust, waste incineration, and second-hand smoke.

2.2 SUMMARY OF HEALTH EFFECTS

Information about the effects of cresols in humans is derived mainly from case reports of accidental or intentional ingestion of cresol solutions or from accidental contact of cresol with the skin. Cresols produce corrosive damage at sites of contact; therefore, the skin and mucosal membranes are targets for cresols toxicity. In a single study of controlled exposures in volunteers, brief exposures to 6 mg/m^3 *o*-cresol caused 8 out of 10 subjects to complain of respiratory irritation. Fatalities due to ingestion and dermal exposure to cresols have been described. Other effects reported in these acute high oral and/or dermal exposure scenarios include respiratory failure, tachycardia and ventricular fibrillation, abdominal pain, vomiting, and corrosive lesions of the gastrointestinal tract, methemoglobinemia, leukocytosis and hemolysis, hepatocellular injury, renal alterations, skin damage, metabolic acidosis, and unconsciousness. Many of these effects may not have been caused directly by cresols, but represent secondary reactions to shock caused by external and internal burns.

Inhalation or dermal exposure of animals to cresols has produced irritation and corrosion at the site of contact. Animals exposed acutely to cresol vapors and aerosols showed signs of respiratory irritation, although the levels associated with irritation have not been reliably documented. Inflammation and irritation of the upper respiratory tract, pulmonary edema, and hemorrhage and perivascular sclerosis in the lungs were seen in a variety of animal species exposed intermittently to 9–50 mg/m^3 of *o*-cresol for ≥1 month; other isomers were not tested. White mice exposed acutely to commercial mixtures of cresol isomers exhibited irritation and inflammation of the eyes and nose. Also noticed in these inhalation studies were effects on the nervous system (excitation, fatigue, convulsions). Animals that died had fatty

degeneration and necrosis of the liver, degeneration of the tubular epithelium in the kidneys, bronchitis, pulmonary hemorrhage, and dystrophic changes in the heart and in nerve cells and glia in the brain. All three cresol isomers, either alone or in combination, severely irritated the skin of rabbits, producing visible and irreversible tissue destruction.

From a limited number of intermediate oral studies, nasal epithelial lesions appear to be a particularly sensitive target for cresols' toxicity. Dietary exposure of rats and mice to *p*-cresol or to a mixture of *m/p*-cresol (58.5% *m*-cresol, 40.9% *p*-cresol) for 28 days or 13 weeks induced dose-related alterations in the nasal respiratory epithelium at doses of 95 mg/kg/day and higher. The severity of the lesions also was dose-related. The lesions were located at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. No such lesions were seen with *o*- or *m*-cresol in the 28-day study or with *o*-cresol in the 13-week study (neither *m*-cresol nor *p*-cresol alone were tested in the 13-week study). Intermediate-duration oral gavage studies and two multi-generation reproductive dietary studies in mice did not examine the nasal respiratory epithelium of the animals. It is also relevant to note that in the inhalation studies discussed above, there is no specific mention of evaluation of the nasal cavity. Additional studies may be necessary to rule out the possibility that the nasal lesions are due to direct contact of cresol with the nasal epithelium (see Section 2.3 for a more detailed discussion on this particular issue).

The nervous system also appears to be a sensitive target of cresols toxicity in oral studies, although this seems to be limited to oral gavage studies. Rodents administered cresols by oral gavage for acute or intermediate durations showed neurological signs such as hypoactivity, excessive salivation, labored respiration, and tremors, in addition to decreased body weight gain. Some neurological signs were observed in rats dosed by gavage with as low as 50 mg/kg/day of cresol isomers. None of these effects have been seen in dietary studies, or if seen, they have occurred at much higher dose levels than in oral gavage studies. The reason for this difference is unknown, but it probably is related to the different disposition of cresols and metabolites between the two modes of oral dosing.

Dietary exposure to higher doses of cresols, generally >240 mg/kg/day, caused increases in liver weight; thresholds for these changes in liver weight were comparable among cresol isomers. Kidney weight was only increased in rats dosed with ≥861 mg/kg/day *o*-cresol for 28 days. Clinical chemistry tests gave no indication of altered function in these organs and no gross and microscopic alterations were seen, even at the highest doses administered (>1,000 mg/kg/day). Other systemic effects observed in rats and mice

treated with relatively high doses of cresols (>1,000 mg/kg/day) in the diet included decreased weight gain (all isomers).

Reproductive effects of cresols isomers administered to rats and mice in the diet were limited to mild to moderate uterine atrophy and lengthening of the estrous cycle, generally at the highest dose levels tested (>2,000 mg/kg/day). Dietary multi-generation studies in mice with *o*-cresol and *m/p*-cresol found no significant effects with *o*-cresol; *m/p*-cresol at the highest level tested (1,682 mg/kg/day), caused minor maternal toxicity (reduced body weight gain), decreased number of pups/litter, and increased cumulative days to litter (delay in producing additional F_1 offspring). Developmental studies that treated rats and rabbits by oral gavage during gestation observed fetal effects (skeletal variations and delayed ossification) at dose levels that also caused maternal toxicity.

No standard 2-year bioassays have been conducted to evaluate the carcinogenic potential of cresols. Cresols gave indications of promotion potential in a dermal skin promotion assay; *p*-cresol was the least potent isomer, *o*-cresol was approximately 3 times more potent than *p*-cresol, and *m*-cresol was in between. The EPA has determined that cresols are possible human carcinogens (Group C) based on inadequate data in humans and limited data in animals (the assessment is dated 10/89). According to EPA's updated criteria for classifying chemicals, cresols fall in the category of chemicals for which there is "inadequate information to assess carcinogenic potential."

The database in animals is insufficient to propose a toxicity ranking for cresol isomers, even though *p*-cresol seemed to be the most potent for induction of the critical effect, nasal respiratory lesions, in rats and mice in the NTP study. The human database is inadequate to propose a toxicity ranking for cresol isomers.

2.3 MINIMAL RISK LEVELS (MRLs)

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for cresols. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for

acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990a), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

Inhalation MRLs

The available health effects data for humans or animals exposed to cresols by inhalation are inadequate to establish concentration-response relationships, which are needed to identify adverse effects levels. Therefore, inhalation MRLs were not derived for cresols. In an experiment in humans, brief exposures to 6 mg/m^3 *o*-cresol caused 8 out of 10 subjects to complain of respiratory irritation (Uzhdavini et al. 1972). No information was provided on how the cresol vapor was generated or sampled. Two animal studies were available in which exposure involved mixtures of vapors and aerosols that provided insufficient information to reliable estimate exposure levels (Campbell 1941; Uzhdavini et al. 1972). *o*-Cresol (9–50 mg/m^3) was tested in the studies of Uzhdavini et al. (1972) in a variety of species, whereas Campbell et al. (1941) tested commercial mixtures of cresol isomers in white mice. These studies provided data on lethality, as well as information on effects on the respiratory system (irritation, inflammation, edema, hemorrhage), and nervous system (excitation, fatigue, convulsions). Animals that died had fatty degeneration and necrosis of the liver, degeneration of the tubular epithelium in the kidneys, bronchitis, pulmonary hemorrhage, and dystrophic changes in the heart and in nerve cells and glia in the brain. Because of limitations in study design (mainly in the methodology for generating and monitoring the vapor concentrations) and reporting, these studies are not useful for risk assessment.

Oral MRLs

As mentioned in Section 2.2, effects of cresol administered by oral gavage are markedly different than those observed in dietary studies. Administration of cresols by oral gavage to animals results in lowest-observed-adverse-effect levels (LOAELs) much lower than LOAELs defined in dietary studies. For

example, LD_{50} values for undiluted cresols in rats ranged from 121 to 242 mg/kg/day (EI Dupont 1969), whereas dietary doses in the range of 1,000–2,000 mg/kg/day for intermediate durations caused little or no toxicity in rats and mice (NTP 1992b). Serious neurological effects (i.e., lethargy, tremors, convulsions) were seen in rats dosed by oral gavage with doses ranging from 450 to 600 mg/kg/day for 90 days (EPA 1988b, 1988c, 1988d; TRL 1986; Tyl 1988a, 1988b), but no such effects were observed in the dietary studies at much higher dose levels (NTP 1992a, 1992b, 1992c). The reason for this difference is not known, but it is most likely related to differences in toxicokinetics between the two routes of exposure. There are no studies that compared the toxicokinetics of cresols following dietary and gavage administration, but there is information for a related chemical, phenol. Phenol toxicity following oral gavage dosing is different than following administration in the drinking water. In the case of phenol, there are data that suggest that toxicity is correlated with peak blood concentration rather than with total dose, such as the area under the blood concentration curve (AUC) following a single gavage dose or repeated daily doses. This is consistent with data from Bray et al. (1950), who observed that *p*-cresol was more toxic when given by stomach tube to fasting rabbits than when the rabbits were given their daily food 1–2 hours before dosing with *p*-cresol; the assumption is that *p*-cresol became mixed with the food, which delayed its absorption. Also relevant is a recent study by Morinaga et al. (2004), which found concentrations of free cresols in liver and spleen from rats given a single oral gavage dose much higher than in blood at all times after dosing (up to 8 hours). This led the investigators to suggest that cresol administered via a stomach tube diffuses directly though the gastric and small intestinal walls, which would explain the very high concentration found in the liver and also in the spleen, which is adjacent to the stomach. Based on these observations and the fact that an oral gavage exposure protocol does not resemble human environmental exposure scenarios to cresols, only dietary studies are considered for MRL derivation, even though some LOAELs by gavage are lower than dietary LOAELs.

No acute-duration oral MRL was derived for cresols due to lack of acute dietary exposure studies.

- An MRL of 0.1 mg/kg/day has been derived for intermediate-duration oral exposure (15–364 days) to cresols.

Almost all of the information available on health effects from intermediate-duration oral exposure is derived from a comprehensive study in rats and mice administered *o*-, *m*-, or *p*-cresol or a cresol mixture of *m*- and *p*-cresol for 28 days or 13 weeks (NTP 1992b). There are also two multigeneration reproductive toxicity studies in mice dosed with *o*-cresol (NTP 1992a) and a mixture of *m*- and *p*-cresol (NTP 1992c). In the NTP (1992b) study, rats and mice dosed with *p*-cresol or an *m/p*-cresol mixture showed lesions in the nasal respiratory epithelium. The nasal lesions occurred in rats dosed with *p*-cresol

for 28 days (≥770 mg/kg/day), in rats exposed to *m/p*-cresol for 28 days (≥95 mg/kg/day), in mice exposed to *p*-cresol for 28 days (≥163 mg/kg/day), in mice exposed to *m/p*-cresol for 28 days (≥604 mg/kg/day), in rats exposed to *m/p*-cresol for 13 weeks (≥123 mg/kg/day), and in mice exposed to *m/p*-cresol for 13 weeks (≥472 mg/kg/day). The lesions were located at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. The hyperplasia was characterized by increased number of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. The hyperplastic areas were associated with single cell necrosis. The intermediate-duration oral gavage studies (EPA 1988b, 1988d) and two multi-generation reproductive dietary studies in mice (NTP 1992a, 1992c) did not examine the nasal respiratory epithelium of the animals. Small increases in liver weight were observed in rats and mice at higher doses (≥242 mg/kg/day) in both the 28-day and 13-week studies; kidney weight was only increased in rats dosed with ≥861 mg/kg/day *o*-cresol for 28 days. However, the changes in organ weight were not associated with alterations in clinical tests of liver and kidney function or gross and microscopic alterations (NTP 1992b). Decreased weight gain was also observed in rats and mice at relatively high doses (>1,000 mg/kg/day).

In addition to the systemic effects observed in the 28-day and 13-week studies (NTP 1992b), exposure to high doses of cresols has resulted in reproductive and developmental effects. Mild to moderate uterine atrophy and lengthening of the estrous cycle were generally observed at the highest dose levels tested (>2,000 mg/kg/day) for all three isomers. Exposure of mice to 1,682 mg/kg/day *m/p*-cresol caused minor maternal toxicity (reduced body weight gain), decreased number of pups/litter, and increased cumulative days to litter (delay in producing additional F_1 offspring). These effects were not observed in mice exposed to 660 mg/kg/day *o*-cresol (NTP 1992a).

Evaluation of the results of the available intermediate-duration dietary studies indicates that the most sensitive end point was the nasal respiratory epithelium of rats and mice dosed with *p*-cresol or a mixture of *m*- and *p*-cresol (NTP 1992b). The effects occurred in male and female rats and mice dosed for 28 days or 13 weeks. The data sets considered for MRL derivation were the 28-day experiment in female rats and the 13-week experiment in male rats based on the lowest effect levels identified in both sets, 95 mg/kg/day in the 28-day experiment and 123 mg/kg/day in the 13-week experiment. In the 28-day study, the incidences of hyperplasia of the nasal respiratory epithelium in female rats dosed with 0, 27, 95, 268, 886, and 2,570 mg/kg/day of *m/p*-cresol were 0/5, 0/5, 3/4, 5/5, 5/5, and 5/5, respectively. In the 13-week study, the incidences in male rats dosed with 0, 123, 241, 486, 991, and 2,014 mg/kg/day *m/p*-cresol were 0/10, 3/10, 8/10, 10/10, 8/10, and 10/10, respectively. The latter series is preferred

because of the longer duration of exposure and because of the increased reliability of a dose-response curve based on 10 rats per group rather than on only 5 rats per group in the 28-day study.

An issue that has to be considered is the possibility that the nasal lesions were caused by evaporation of the cresol from the food (even though cresols have relatively low vapor pressure, particularly *p*-cresol) and thus due to direct contact of the airborne chemical with the nasal respiratory epithelium. The inhalation database consists of a study by Uzhdavini et al. (1972) who exposed various animal species to *o*-cresol (*o*-cresol did not induce nasal lesions in the NTP study) for various periods of time. Acute exposures of mice produced irritation of mucous membranes and higher concentrations induced pulmonary edema and histopathological changes in the lungs. Repeated exposures of mice also induced symptoms of irritation of the respiratory tract, but there is no specific mention of the nasal cavity. Exposures of rats and guinea pigs for 4 months produced symptoms of irritation and inflammation in the upper respiratory tract, local edema, and perivascular sclerosis in the lungs. Because of limitations in study design and reporting, few conclusions can be drawn from the experiments of Uzhdavini et al. (1972) other than that *o*-cresol is a respiratory irritant at the concentrations tested. NTP (1992b) conducted preliminary studies to assess the stability of the various cresol isomer-feed mixtures and detected losses due to evaporation from 10 to 12% after storage for 7 days under simulated cage conditions. Therefore, fresh chemical-diet mixtures were supplied twice weekly during the studies. Estimating the concentration of cresol in the air from such losses from food is virtually impossible due to numerous uncertainties. The threshold for nasal lesions in rats was about 2,000 mg/kg of *m/p*-cresol in the food. A loss of 10% per week represents 200 mg of cresol/kg of food per week or about 1.2 mg/kg feed per hour. However, a concentration of cresol in air cannot be estimated because of many unknown factors such as volume of distribution, air flow speed, etc. A somewhat related possibility is that cresol evaporates inside the mouth of the animal aided by the higher temperature (about 38 °C) and reaches the nasal cavity from inside the mouth. There is also the possibility of nasal exposures due to exhalation of the cresols previously ingested, although there is no indication from toxicokinetics studies that this may occur. Until it can be demonstrated with some certainty that the nasal lesions are not caused by a systemic effect of cresol and in the interest of protecting humans potentially exposed under similar conditions, the MRL was based on the increased incidence of the nasal lesions in rats.

In the principal study for the MRL, groups of Fischer 344 rats (20/sex/group) were administered *m/p*-cresol (58.5% *m*-cresol, 40.9% *p*-cresol) in the diet at levels of 0, 1,880, 3,750, 7,500, 15,000, or 30,000 ppm for 13 weeks (NTP 1992b). The corresponding doses of test compound estimated by the investigators were 0, 123, 241, 486, 991, and 2,014 mg/kg/day for males and 0, 131, 254, 509, 1,024, and

2,050 mg/kg/day for females. End points evaluated included clinical signs, food consumption, organ weights, clinical chemistry and hematology, and gross and microscopic appearance of organs and tissues. Although the dose groups consisted of 20 rats of each sex, 10 males and 10 females were used for clinical chemistry, hematology, and urinalysis studies and the remaining 10 rats/sex/group were used in gross pathology, organ weight, and histopathological studies. There were no deaths during the study. Final body weight in the 2,014/2,050 mg/kg/day males and females was reduced 17 and 12%, respectively, relative to controls. Food consumption was also reduced (about 10%) in this group during the first week of the study. Additionally, males and females in this group exhibited rough hair coat; females also had a thin appearance. Absolute and relative liver weights were significantly increased (11–12%) in males at 486 mg/kg/day and in females at 1,024 mg/kg/day. Absolute and relative kidney weight was increased in males at 991 mg/kg/day. In general, hematology findings were unremarkable, although there was a tendency to hemoconcentration at 2,014/2,050 mg/kg/day early in the study. Clinical chemistry tests showed an increase in serum alanine aminotransferase (ALT) in males and females exposed to 2,014/2,050 mg/kg/day and in sorbitol dehydrogenase (SDH) in males at 2,014 mg/kg/day only on day 5. Bile acids in serum were increased in females at 2,050 mg/kg/day on day 90 and at 241 and 991 mg/kg/day in males also on day 90. There was no indication of renal injury as judged by the results of urinalyses. Significant histopathological changes included minimal bone marrow hypocellularity in males and females (likely secondary to decreased weight gain) at 2,014/2,050 mg/kg/day, and increased colloid (minimal) in thyroid follicular cells in females at 509 mg/kg/day and in males at 15,000 ppm (991 mg/kg/day). An increased dose-related incidence and severity of hyperplasia and glandular hyperplasia of the nasal respiratory epithelium was observed in male and female rats. Severity was minimal at 123/131 mg/kg/day, mild at 486/509 mg/kg/day, and moderate at 2,014/2,050 mg/kg/day. The lesions were located at the most anterior portions of the nasal septum, dorsal arch, and medial aspect of the nasal turbinates. The hyperplasia was characterized by increased number of goblet cells and pseudogland formation due to the infolding of the hyperplastic cells. The hyperplastic areas were associated with single cell necrosis. The incidences in males dosed with 0, 123, 241, 486, 991, and 2,014 mg/kg/day were 0/10, 3/10, 8/10, 10/10, 8/10, and 10/10, respectively. A similar trend was seen in female rats, but 3/10 control females also exhibited hyperplasia (3/10, 1/10, 5/10, 9/10, 8/10, and 10/10 at 0, 131, 254, 509, 1,024, and 2,050 mg/kg/day, respectively).

Data from the NTP (1992b) were considered adequate for analysis using the benchmark dose approach for MRL derivation. Benchmark dose models in the EPA Benchmark Dose Software (BMDS) (version 1.3.2) were fit to the incidence data for nasal lesions in male and female rats exposed to *m/p*-cresol in the diet for 13 weeks in order to determine potential points of departure for the MRL

(details of the modeling are presented in Appendix A). Comparing fits across nine different models, the log-logistic model was determined to be the best-fitting model for the male rat data set, whereas the quantal linear model was the best-fitting model for the female rat data set. Following EPA's Benchmark Dose Guidance (EPA 2000a) to select a point of departure, a benchmark response (BMR) of 10% was selected for the benchmark analysis of nasal lesion incidence data in the 13-week NTP (1992b) study. The BMD corresponding to a BMR of 10% extra risk is 55.89 mg/kg/day. $BMDL_{10}$s (i.e., 95% lower confidence limits on the model-estimated dose associated with a 10% extra risk for nasal lesions) calculated with the best-fitting models for each data set were 13.9 mg/kg/day for males and 30.8 mg/kg/day for females. While this difference in benchmark dose may indicate that male rats are more sensitive than females, it also can be just a statistical artifact in a rather small sample size, only 10 rats per group. The male rat data set was selected for determining the point of departure for MRL derivation in order to be public health protective. Applying an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability) to the $BMDL_{10}$ of 13.9 mg/kg/day yields an intermediate-duration oral MRL of 0.1 mg/kg/day for *m/p*-cresol.

For the purpose of comparison, using a no-observed-adverse-effect level (NOAEL)/LOAEL approach, the dose of 123 mg/kg/day, which was associated with an incidence of 3/10 in male rats, can be considered a minimal LOAEL for the following reasons: (1) the severity of the lesion was categorized as *minimal*, (2) pairwise comparison with controls using Fisher's Exact Test yields marginal significance ($p=0.105$) and the Cochran-Armitage Trend Test is highly significant ($p<0.0001$), and (3) three out of four female rats dosed with 95 mg/kg/day of *m/p*-cresol for 28 days showed *minimal* nasal hyperplasia. Applying an uncertainty factor of 300 (3 for a minimal LOAEL, 10 for animal to human extrapolation, and 10 for human variability) to the LOAEL of 123 mg/kg/day yields an intermediate-duration oral MRL of 0.4 mg/kg/day.

The most comprehensive study of cresols by dietary exposure is the NTP (1992b) study. In that study, each individual isomer and an *m/p*-cresol mixture were tested in rats and mice for 28 days; in addition, *o*-cresol and *m/p*-cresol were tested in rats and mice for 13 weeks. Assessing the comparative toxicity of the cresol isomers, NTP (1992b) noted that: "In general, there were no significant indications of distinct toxicities between the three isomers." However, nasal lesions only occurred in rats and mice dosed with *p*-cresol and *m/p*-cresol in the 28-day studies and in rats and mice dosed with *m/p*-cresol in the 13-week studies. Since *m*-cresol alone was not tested in the 13-week studies, it is unknown whether longer dietary exposure to this isomer would produce similar lesions. Thus, it would appear that *p*-cresol is the most toxic of the isomers with regard to inducing nasal lesions and, since no other significant toxicities were

observed in these dietary studies, the MRL for *m/p*-cresol should also be protective for exposures to the individual cresol isomers. Therefore, the intermediate-duration oral MRL for *m/p*-cresol also can be adopted for *o*-, *m*-, and *p*-cresol.

No chronic-duration oral MRLs were derived for cresols due to lack of chronic data by any route of exposure.