# ADDENDUM TO THE TOXICOLOGICAL PROFILE FOR CHLOROPHENOLS

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# ADDENDUM FOR CHLOROPHENOLS
## Supplement to the 1999 Toxicological Profile for Chlorophenols

### Background Statement

*This addendum to the Toxicological Profile for Chlorophenols supplements the profile that was released in 1999.*

*Toxicological profiles are developed in response to the Superfund Amendments and Reauthorization Act (SARA) of 1986 which amended the Comprehensive Environmental Response, Compensation, and Liability Act of 1980 (CERCLA or Superfund). CERCLA mandates that the Administrator of ATSDR prepare toxicological profiles on substances on the CERCLA Priority List of Hazardous Substances and that the profiles be revised "no less often than once every three years." CERCLA further states that the Administrator will "establish and maintain an inventory of literature, research, and studies on the health effects of toxic substances" [Title 42, Chapter 103, Subchapter I, § 9604 (i)(1)(B)].*

*The purpose of this addendum is to provide to the public and to federal, state, and local agencies a non-peer reviewed supplement of the scientific data that were published in the open peer-reviewed literature since the release of the profile in 1999.*

*Chapter numbers in this addendum coincide with the Toxicological Profile for Chlorophenols (1999). This document should be used in conjunction with the profile. It does not replace it.*

# 2. HEALTH EFFECTS

## 2.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

### 2.2.1 Inhalation Exposure

#### 2.2.1.5 Reproductive Effects

An epidemiological study investigated low birth weight of small-for-gestational-age (SGA) infants whose mothers were occupationally exposed to chlorophenols (Seidler et al. 1999). The cohort consisted of 3,946 German women recruited during weeks 15 to 28 of pregnancy. The SGA outcome was defined as a birth weight below the $10^{th}$ percentile for sex-specific gestational age, based on 563,480 infant births recorded in Germany during 1992 (Voigt et al. 1996). The results showed that 9.5% (9.9% of males and 9.0% of females) of the 3,216 infants with completed outcome data were classified as SGA (Seidler et al. 1999), which is consistent with expectations for the $10^{th}$ percentile group. Occupational exposures to chlorophenols and other chemicals such as carbon tetrachloride, polychlorinated biphenyls, lead, mercury, and aromatic amines were estimated at the work places for each mother based on a job-exposure-matrix (Pannet et al. 1985). The job-exposure-matrix was used to assign chemical exposure categories (low, moderate, high) to job categories. Specifically, an exposure score below 1 was considered no exposure, an exposure score $\geq 1$ but $< 2$ was low exposure, an exposure score $\geq 2$ but $< 3$ was moderate exposure, and an exposure score $\geq 3$ was considered as high exposure (Seidler, et al. 1999). Information on occupation and other demographic, nutritional, and environmental factors was obtained from a self-administered questionnaire. A group of 1,351 unemployed women served as a control group, and odds ratios (ORs) were adjusted for age, smoking, alcohol consumption, body mass index, number of previous births, and household income. The adjusted OR for infants classified as SGA was significant for subjects with moderate exposure to chlorophenols [OR 7.0; 95% CI (1.2 to 43.0)], which was the highest exposure category reported for chlorophenols. The results for the high dose exposure category for chlorophenols were not reported in this study. The OR increased significantly as the exposure score increased from low (4.1; 95% CI 0.3-48.3) to moderate. (7.0; 95% CI 1.2 to 43.0). The authors suggested that this study may have been affected by several confounding variables including exposure misclassification from the application of the job-exposure-matrix and recognized co-exposures to other chemicals. The authors also suggested that continued research is necessary to elucidate any potential chlorophenols-induced maternal influences on the risk of this birth outcome (SGA) (Seidler et al. 1999).

#### 2.2.1.8 Cancer

Three studies investigated a possible link between occupational exposures to chlorophenols and cancer morbidity i.e, soft tissue sarcoma (Hoppin et al. 1998), nasopharyngeal (Mirabelli et al. 2000, and non-

Hodgkin's lymphoma (Garabedian et al.1999). Exposure information was obtained via telephone interviews of cases and controls with questions about job history. The information was used to classify exposure by job type as a combination of exposure intensity, level of confidence with exposure intensity assignment, and potential for both dermal and inhalation exposure. The cases and controls were placed in categories of unexposed, minimal exposure, moderate exposure, and substantial exposure. Adjusted ORs were based on a total of 295 cases and 1,908 controls. ORs for strictly defined soft tissue sarcomas were estimated for all exposure categories and were controlled for age, registry (40 matching strata), ethnicity, medical radiation, chemotherapy, and herbicide use (Hoppin et al. 1998). The risk of soft tissue sarcoma increased significantly as the exposure duration equaled or exceeded 5 years, and especially 10 years (OR 7.8; 95% CI 2.5 to 24.6; 6 cases, 7 controls) (Hoppin et al. 1998).

Another occupational study investigated a link between chlorophenols and nasopharyngeal cancer. Information in this study was obtained by interviewing 43 nasal carcinoma cases, 92 nasopharyngeal carcinomas cases, and 1,909 controls. Cases were adjusted for age and registry (matching factors), race/ethnicity, and smoking history. Mirabelli et al. (2000) found an increased risk of nasopharyngeal cancers for workers placed in the medium chlorophenols exposed group; adjusted OR (1.94; 95% CI; 1.03 to 3.50; 18 exposed cases; 244 controls) and the high exposed group (2.64; 95% CI 1.11 to 5.78) with increasing exposure duration (OR > 10 years 9.07; 95% CI; 1.41 to 42.9; 3 exposed cases; 7 controls). Other exposure variables that were not found to influence the OR included household income and education, history of mononucleosis or sinus problems, alcohol consumption, and exposure to solvents, chlorophenoxy herbicides, formaldehyde, and wood and/or saw dust (Mirabelli et al. 2000).

Garabedian et al. (1999) investigated a potential risk of non-Hodgkin's lymphoma in workers who were exposed to chlorophenols using data from 995 cases and 1,783 controls. The data were adjusted for age, registry (matching factors), ethnicity, education level, smoking history, and risk factors for acquired immune deficiency syndrome. The adjusted OR for "ever being occupationally exposed to low, medium, or high concentrations of chlorophenols with medium or high confidence levels" was 1.07 (95% CI 0.93 to1.24; 255 cases, 399 controls), and when exposure durations were restricted to >8 years, the OR increased to 1.51 (95% CI 0.88 to 2.59; 18 cases, 8 controls). No information was provided on route of exposure. The authors suggested that this study may not be reliable since the results were not based on measured indoor air levels of chlorophenols. Furthermore, the authors indicated that there was insufficient evidence to support a conclusion of increased risk of non-Hodgkin's lymphoma from exposure to chlorophenols.

A retrospective cohort study was conducted by Demers et al. (2006) on past exposures to chlorophenols (pentachlorophenol and 2,3,4,6-tetrachlorophenol) and cancer morbidity and mortality in sawmill workers in British Columbia, Canada. The cohort consisted of 27,464 former male workers who were employed

at 14 different sawmills during the period from1950 to 1995. The authors noted that exposure to chlorophenols in the sawmill industry occurs primarily from inhalation and dermal absorption. Cancers that occurred during the period from 1969 to 1995 were identified from records in cancer registries. Exposures to chlorophenols were estimated from records of uses and practices of chlorophenols containing fungicides at each sawmill for each subject, and interviews of older workers regarding work processes for each job. This information was used to assign subjects to exposure index categories (e.g., exposure duration as exposure-years, where 1 exposure-year was equivalent to 2,000 hours of exposure). Age-adjusted standard incidence ratios (SIRs) and standard mortality ratios (SMRs) were estimated based on cancer incidence and mortality data for British Columbia as the reference population using a life table analysis. A total of 1,495 cancer fatalities from 2,471 incidence cases were recorded for the cohort. Estimated SIRs and SMRs were not significant for the specific cancers reported i.e., soft tissue carcinoma, nasopharyngeal cancer, non-Hodgkin's lymphoma, multiple myeloma, lung cancer, and kidney cancer. The highest risks observed were for multiple myeloma, for which the mortality relative risk (RR) for ≥5 exposure-years to pentachlorophenol was 4.80 (95% CI 1.39 to 6.54), and the RR for incidence was 4.18 (95% CI 1.36 to 12.9). This study provided some evidence for possible associations between exposure to pentachlorophenol and the risk of kidney cancer, non-Hodgkin's lymphoma, and multiple myeloma. However, no evidence was found to link 2,3,4,6-tetrachlorophenol, or other chlorophenols, exposure to these abnormalities. The observation of significant risks in association with pentachlorophenol exposure, but not 2,3,4,6-tetrachlorophenol, is also potentially relevant to the interpretation of other studies that have found significant risks associated with exposures to chlorophenols (e.g., Hoppin et al. 1998; and Mirabelli et al. 2000), as it is suggested that at least some or all of the observed risks may be attributable to exposure to pentachlorophenol. Previous studies provided evidence of possible links between chlorophenols exposure and increased risk of soft tissue sarcoma (Hoppin et al. 1998), and nasopharyngeal cancer (Mirabelli et al. 2000). However, several uncertainties precluded drawing definitive conclusions from these studies, including the potential misclassification of exposure resulting from assigning subjects to categories after exposures ended, use of a post-hoc categorical assignment of subjects to exposure categories rather than using direct measurements, and the potential influence of previous or co-exposures to other chemicals (e.g., solvents, formaldehyde, chromium, nickel). Therefore, these studies do not provide sufficient evidence to attribute an increased risk of soft tissue sarcoma and nasopharyngeal cancer to chlorophenols exposure (Hoppin et al. 1998; and Mirabelli et al. 2000).

### 2.2.2 Oral Exposure

#### 2.2.2.2 Systemic Effects

#### Body Weight Effects

The potential for 2,4-dichlorophenol to adversely affect body weight gain was observed in a two-generation reproductive toxicity study in Wistar-Hanover rats (Aoyama et al. 2005). Groups of 24 rats/sex/group were administered a diet containing 2,4-dichlorophenol at 0, 500, 2,000 or 8,000 ppm which corresponded to 0, 33.4, 134, or 543 mg/kg/day for males and 0, 49.1, 194, or 768 mg/kg/day for females. The parental generation (P) was exposed to diets without 2,4-dichlorophenol, or with 2,4-dichlorophenol for 10 weeks prior to mating and through the gestation and lactation periods, then was sacrificed upon weaning of their offspring. Offspring of the P generation (F1) were exposed to 2,4-dichlorophenol from weaning through mating, gestation, and lactation and were sacrificed upon weaning of their offspring. Offspring of the F1 generation (F2) were sacrificed at weaning. Feed aversion was apparent since body weight gain, and feed consumption were significantly decreased in mid-dose P generation females at the end of the pre-mating, and during the gestational periods, and in high-dose P and F1generation males and females throughout exposure (Aoyama et al. 2005).

#### 2.2.2.4 Neurological Effects

Recently, Xu et al. (2011) calculated odds ratios and 95% confidence intervals from logistic regression analyses utilizing data from the 1999-2004 National Health and Nutrition Examination Survey (NHANES) to determine if an association existed between trichlorophenol exposure and attention deficit disorders in 2,546 children aged 6-15. The children's results were compiled from the parents' answers on questionnaires and not from any medical records. The results showed that children with low (< 3.58 μg/g) and high (≥ 3.58 μg/g) levels of trichlorophenol in urine samples had a higher risk of parent reported attention deficit disorder than children with urinary trichlorophenol levels below the levels of instrumentation detection. Trichlorophenol detected in urine samples represent recent exposures which may have increased the risks of behavioral impairment in children. The developing central nervous systems of growing children may be especially vulnerable to environmental contaminants that interfere with neurotransmitters synthesis, storage, degradation, or re-uptake into the presynaptic nerve terminal. Environmental contaminants that cause these neurotransmitters effects may also alter intracellular signaling resulting in behavioral impairments such as attention deficit disorder [Xu et al. 2001].

Hasegawa et al. (2005) conducted an animal study that compared the susceptibilities of newborn rats to those of young rats for six industrial chemicals, including 2-chlorophenol, and 4-chlorophenol (Hasegawa et al. 2005). The neurotoxic parameters examined included tremors, hypo-activity, abnormal gait,

salivation, and tachypnea. The comparative susceptibility of newborn rats to young rats exposed to 2-chlorophenol or 4-chlorophenol was measured by two different toxicity endpoints. The investigators used a "presumed" no-observed-adverse-effect-level (p-NOAEL) and a "presumed" unequivocally toxic level (p-UETL). They defined the p-NOAEL as that level of chemical exposure for which no adverse effects were observed, and the p-UETL as that level of chemical exposure which clearly induced clinical signs of toxicity. Animals from different treatment groups received gavage-intubation of different chemicals under the same experimental conditions as closely as possible (Hasegawa et al. 2005).

Newborn rats (12/sex/group) were administered 2-chlorophenol at doses of 0, 20, 50, 100 or 300 mg/kg/day, or 4-chlorophenol at doses of 0, 60, 100, or 300 mg/kg/day in olive oil by oral-gavage on postnatal days (PDs) 4 to 21. Statistically significant increases in tremors (11/12 males, 12/12 females) were observed in newborn rats treated with 300 mg/kg of 2-chlorophenol, while few signs of hypo-activity and abnormal gait were observed (Hasegawa, 2005). The clinical signs of neurotoxicity appeared within 5 minutes of dosing and vanished approximately 4 hours post-exposure. Clinical signs of neurotoxicity were not observed in newborn control rats, or at lower doses (20, or 100 mg/kg/day) of 2-chlorophenol exposure (one female exhibited tremors at 50 mg/kg/day). Similarly, newborn rats of both sexes treated with 300 mg/kg of 4-chlorophenol revealed tremors (12/12), but not at 60 or 100 mg/kg/day. Tremors occurred approximately 15 to 60 minutes after dosing and disappeared within 4 hours post-exposure. Newborn rats exposed to 4-chlorophenol at 300 mg/kg/day also revealed rapid breathing and salivation (Hasegawa et al. 2005). The remaining newborn rats were maintained in the study for a 9-week non-treatment-recovery period and sacrificed at 12 weeks of age (Hasegawa et al. 2005).

Furthermore, neurological effects were assessed in young (5 to 6 weeks old) male and female Sprague-Dawley rats (12/sex/group) following oral-gavage-dosages of either 2-chlorophenol or 4-chlorophenol. The animals received either 2-chlorophenol at 0, 200, 500, or 1,000 mg/kg/day or 4-chlorophenol at 0, 100, or 500 mg/kg/day in olive oil for 28 days. Young rats treated with 1,000 mg/kg/day of 2-chlorophenol showed tremors (4/12), hypo-activity (8/12), and abnormal gait (4/12). The signs of neurotoxicity appeared approximately three hours after dosing, and times to disappearance of symptoms were not reported. Furthermore, exposure to 2-chlorophenol at 1,000 mg/kg/day revealed centrilobular hepatocyte hypertrophy without gross changes being observed. Young rats of both sexes treated with 500 mg/kg/day 4-chlorophenol showed clinical signs of toxicity which included tremors, rapid breathing, and salivation. The onset of symptoms occurred approximately 5 to 30 minutes after dosing, and the time to disappearance of symptoms was not reported (Hasegawa et al. 2005). A provisional-NOAEL (p-NOAEL) was estimated at 40 mg/kg/day for 2-chlorophenol and was based on tremors observed in only one female rat exposed to 50 mg/kg/day for 18 days. Hasegawa et al. (2005) also derived a 28-day p-NOAEL of 200 mg/kg/day for 2-chlorophenol based on the study in the young rats reporting neurological effects at ≥500 mg/kg/day. The p-NOAEL derived for exposure to 4-chlorophenol in the newborn as well

as young rats was 100 mg/kg/day. The values estimated for p-UETL for 2-chlorophenol in newborn rats was 200 to 250 mg/kg/day, and 300 mg/kg/day for 4-chlorophenol. The p-UETL derived for the young rat study was 1,000 mg/kg/day for 2-chlorphenol and 500 mg/kg/day for 4-chlorophenol. The results of this study showed that newborn rats were two to five times more sensitive to 2-chlorophenol, or 4-chlorophenol than young rats in terms of p-NOAEL and p-UETL following oral-gavage-exposures (Hasegawa, 2005).

#### 2.2.2.5 Reproductive Effects

The potential for 2,4-dichlorophenol to produce adverse reproductive effects was assessed in a two-generation reproductive toxicity study in Wistar-Hanover rats (Aoyama et al. 2005). Groups of 24 rats/sex/group were administered a diet containing 2,4-dichlorophenol at concentrations of 0, 500, 2,000, or 8,000 ppm, which corresponded to doses of 0, 33.4, 134, or 543 mg/kg/day for males and 0**,** 49.1, 194, or 768 mg/kg/day for females. The parental generation (P) was exposed to diets without 2,4-dichlorophenol, or with 2,4-dichlorophenol for 10 weeks prior to mating and through the gestation and lactation periods, then sacrificed upon weaning of their offspring. Offspring of the P generation (F1) were exposed to 2,4-dichlorophenol from weaning through mating, gestation, and lactation and were sacrificed upon weaning of their offspring. Offspring of the F1 generation (F2) were sacrificed at weaning. Body weight gain and feed consumption were significantly decreased in mid-dose P generation females during the pre-mating and gestational periods, and in high-dose P and F1generation males and females throughout exposure. A statistically significant decrease in the number of implantation sites per female in F1 rats was detected in the high-dose (8,000 ppm or 768 mg/kg/day) group (10.2±3.1, $p \leq 0.05$) compared to controls (12.7±1.8), but not at the 500 ppm and 2,000 ppm or 194 and 768 mg/kg/day doses. No statistically significant effect on the number of implantation sites was observed in the P generation animals. No treatment-related reproductive effects were observed in the P or F1 generations for estrous cycle length, incidence of normal estrous cycles, number of primordial ovarian follicles, mating index, fertility index, gestation index, gestation length, pup number, viability at birth, or sex ratio, or pup viability during lactation. No treatment-related changes were observed in serum hormones that affect the reproductive system (follicle stimulating hormone, luteinizing hormone, prolactin, estradiol, and progesterone) in female rats (assessed in F1 rats only) or for sperm parameters (number of testicular or epididymis sperm, sperm motility, and sperm morphology) in P and F1 males.

#### 2.2.2.6 Developmental Effects

In a two-generation reproductive and developmental toxicity study, 2,4-dichlorophenol was administered in the diets of Wistar-Hanover rats and sexual and physical development was assessed (Aoyama et al. (2005). Groups of 24 rats/sex/group were administered 2,4-dichlorophenol at 0, 500 (low), 2,000 (mid)

and 8,000 (high) ppm in their diets which corresponded to doses of 0, 33.4, 134, or 543 mg/kg/day for males and 0**,** 49.1, 194, or 768 mg/kg/day for females. The parental generation (P) was exposed to diets without 2,4-dichlorophenol, or with 2,4-dichlorophenol for 10 weeks prior to mating and through the gestation and lactation periods, then were sacrificed upon weaning of their offspring. Gross examination of the abdominal and genital regions showed that the incidence of soiled fur was significantly increased ($p \leq 0.05–0.001$) in all high-dose P and F1 males and females. The incidence of increased mammary gland swelling was significantly increased in all 2,4-dichlorophenol P and F1 generation females after weaning of their pups. Swelling resolved within a few days after weaning in the P generation but was not assessed in the F1 generation. Mammary gland whiteness and stiffening incidence was significantly increased in the high-dose (8,000 ppm or 768 mg/kg/day) P females (1/24 controls; 8/24 high-dose animals, $p \leq 0.05$) and in F1 females in all (500, 2000, and 8,000 ppm or 49.1, 194, 768 mg/kg/day, respectively) 2,4-dichlorophenol-treated groups (2/24 controls; 13/24 low-dose animals, $p \leq 0.001$; 16/24 mid-dose animals, $p \leq 0.001$; 18/24 high-dose animals, $p \leq 0.001$). The percentage of pups with eye opening on lactation day 14 was significantly decreased in the high-dose (8,000 ppm or 768 mg/kg/day) F1pups (males 51.7%, $p \leq 0.001$; females 65.3%, $p \leq 0.001$) and F2 pups (males 50.5%, $p \leq 0.05$; females 52.3%, $p \leq 0.001$) compared to their respective controls (F1 males 91.3%; F1 females 94.6%; F2 males 89.1%; F2 females 93.5%). In F1 pups, time to sexual development in females was altered in the high-dose (8,000 ppm) group, with the time to vaginal opening decreasing by approximately 12% ($p \leq 0.05$), compared to controls. Uterine weight was significantly increased in high-dose (8,000 ppm) F1 and F2 weanlings by 42% ($p \leq 0.001$) and 20% ($p \leq 0.05$), respectively. In F2 weanling females, microscopic examination of the uteri showed an increase in epithelial cell height in 7/10 females in the high-dose group compared to 1/10 females in the control group (statistical significance was not reported, and no information reported on microscopic examination of F1 weanling females). In the absence of changes in serum concentrations of pituitary or sex hormones, there were increases in uterine growth in F1 and F2 females, and a slight decrease in implantation sites in live births of P females with significant decreases implantations sites in F1 females (Aoyama et al. 2005).

In another study, Hasegawa et al. (2005) compared developmental sensitivities of newborn rats to 5 to 6 weeks old Sprague-Dawley rats following postnatal exposures to 2-chlorophenol or 4-chlorophenol. Newborn rats (12/sex/group) were administered 2-chlorophenol at doses of 0, 20, 50, 100 or 300 mg/kg/day, or 4-chlorophenol at doses of 0, 60, 100, or 300 mg/kg/day in olive oil by oral-gavage on PNDs 4 to 21. On PND 22, half of the newborn rats were sacrificed for evaluation, and the remaining animals were maintained in the study for a 9-week, non-treatment-recovery period, and sacrificed at 12 weeks of age. Newborn rats were evaluated for developmental milestones (e.g., surface righting, visual reflexes, fur appearance, tooth eruption, eye opening, preputial separation, vaginal opening, and estrous cycle). Macroscopic examinations of newborn rats treated with 300 mg/kg/day of 2-chlorophenol showed an increased incidence of basophilic renal tubules in males and females. However, the statistical

significance was not reported. This finding was not observed in the control or the 50 mg/kg/day dose group and was not assessed in the 20 or 100 mg/kg/day 2-chlorophenol exposed groups. No histopathological effects were observed in newborn or young rats treated with 4-chlorophenol. No adverse effects related to treatment with 2-chlorophenol, or 4-chlorophenol were observed for developmental milestones. No information was reported for newborn, or young rats for examinations conducted after the recovery period. The results of this study reported no significant differences in adverse developmental effects in newborn rats in comparison to controls, or to 5 to 6 week old young rats exposed to 2-chlorophenol or 4-chlorophenol (Hasegawa, et al. 2005).

In the same study, young rats (12/sex/group) were administered 2-chlorophenol at doses of 0, 200, 500, or 1,000 mg/kg/day, or 4-chlorophenol at doses of 0, 100, or 300 mg/kg/day in olive oil by oral-gavage for 28 days. After the treatment period half of the animals were sacrificed for evaluation while the remaining animals were maintained in the study for a 2-week non-treatment recovery period and then sacrificed (11 to 12 weeks of age). At sacrifice, macroscopic examinations of selected tissues (brain, pituitary, thymus, thyroid, heart, lungs, liver, spleen, kidneys, adrenals, testes, epididymides, ovaries, and uterus) were conducted on the 200 and 1000 mg/kg/day dose groups. The only effect noticed was slight centrilobular hypertrophy in the 1000 mg/kg/day dose group. No statistical significance was reported although the finding was not observed in the control group or the 200 mg/kg/day dose group. No histopathological findings were observed in newborn or young rats treated with various doses 4-chlorophenol. No information was reported for newborn, or young rats for examinations conducted after the recovery period. The results of this study reported no significant differences in adverse developmental effects in newborn rats in comparison to controls, or to 5 to 6 week old young rats exposed to 2-chlorophenol or 4-chlorophenol (Hasegawa, et al. 2005).

#### 2.2.2.7 Genotoxic Effects

No mutagenic effects in *in-vivo* and *in-vitro* studies in nuclear magnetic resonance imaged mice were detected using a femoral bone marrow micronucleus assay and the Chinese Hamster Ovary cells test (Tegethoff et al. 2000). Animals received a single oral-gavage of 2,5-dichlorophenol (1,500 mg/kg) in corn oil, and the control group received the same volume of corn oil. Bone marrow micronuclei formation was assessed at 24, 48, and 72 hours post-administration and no mutagenic effects were observed. Similarly, no mutagenic effects were found for 2,5-dichlorophenol in the absence and presence of metabolic activation using an S-9 mix in the CHO cells assay (Tegethoff et al. 2000). The authors suggested that 2,5-dichlorophenol has no mutagenic potential in the present assays used (Tegethoff et al. 2000).

#### 2.2.2.8 Cancer

A study was conducted in Southern Finland to determine if drinking water contaminated with chlorophenols was associated with cancer morbidity (Lampi et al. 2008). At the end of 1987, environmental sampling of groundwater near a village where 2,000 residents lived in Finland revealed chlorophenols levels ranging from 70 micrograms/liter (µg/L) to140 µg/L. The residents used the groundwater as a source of drinking water. The village was located near a saw mill that used fungicides containing chlorophenols which was primarily 2,3,4,6-tetrachlorophenol. The fungicides also contained pentachlorophenol, 2,4,6-trichlorophenol, and other impurities such as polychoro-di-benzo-p-dioxins (PCDDs) and polychloro-di-benzofurans (PCDFs). PCDDs and PCDFs were not detected during groundwater monitoring. Further environmental sampling of the deep aquifer in the vicinity of the saw mill revealed chlorophenols ranging from 56,000 µg/L to 190,000 µg/L. Chlorophenols were detected in a local lake from 2.86 to11.0 µg/L. Fish obtained from the lake revealed chlorophenols from 175 µg/kg (perch) to 925 µg/kg (zander) wet weight. Since the groundwater and fish were contaminated, human exposures to chlorophenols probably occurred from drinking the groundwater and/or eating locally harvested fish. In 1987, the municipal drinking water intakes from groundwater near the area were closed. The epidemiological study indicated that "all the cancer risks returned to the average population level during the 20-year period following the old water intake plant was closed and chlorophenol exposure ceased." The results of this study provided evidence to indicate an association between exposure to chlorophenols and increased risk of soft-tissue-sarcoma and non-Hodgkin's lymphoma. However, these results may have been confounded by several uncertainties: (1) the potential influence of exposures to other chemicals on the outcomes; (2) the potential mixing of environmental and occupational exposures in the analysis; and (3) the absence of a dose-response assessment. The results of this study indicated that soft- tissue-sarcoma and non-Hodgkin's lymphoma incidences returned to near background levels during the 20 year period after the local officials had the water intake plant replaced with a new one, which probably eliminated residential consumption of tap water contaminated with chlorophenols (Lampi et al. 2008).

### 2.2.3 Dermal Exposure

#### 2.2.3.1 Death

Fatalities have been reported in four individual workers following acute accidental exposures to 2,4-dichlorophenol (MMWR 2000). In all cases, the predominant exposure route was dermal. However, some effects in lungs and stomach were noted to have been caused by inhalation. A 29-year-old male chemical plant worker lost consciousness almost immediately and died 1 hour after being sprayed with 2,4-dichlorophenol. Pulmonary edema and chemical burns of exposed skin surfaces were the only findings during autopsy. 2,4- Dichlorophenol levels detected in this patient's blood and urine samples

were 13.1 and 6.2 mg/L, respectively. The cause of death was reported as "acute 2,4-dichlorophenol intoxication."

A 45-year-old male chemical worker died after being sprayed with steam containing 2,4-dichlorophenol. The time elapsed from exposure to death was not reported. Prior to death, the worker experienced loss of consciousness and convulsions. Thermal burns from steam exposure were observed on the skin, mouth, and upper airway, and chemical burns were also observed on the skin. Postmortem findings included pulmonary and laryngeal congestion, alveolar hemorrhage, and hepatocellular fatty change. 2,4-Dichlorophenol concentrations in biological fluids were not reported. The cause of death was reported as "acute steam and dichlorophenol exposure." A 64-year-old chemical worker died 20 minutes after 2,4-dichlorophenol was splashed on his head and neck. No additional information was reported. A 33-year-old chemical worker died approximately 90 minutes after he was splashed over 60% to 65% of his body with a solution containing 51% 2,4-dichlorophenol. Prior to death, the worker experienced loss of consciousness and convulsions. The autopsy revealed significant damage to the lungs with hemorrhagic fluid in both lungs and in stomach, as well as intense congestion and petechial hemorrhages in the brain (MMWR 2000).

#### 2.2.3.8 Cancer

An epidemiological study was conducted in 27,464 men who were previously employed for at least one year in one of 14 different saw mills in British Columbia from 1950 to 1995. The investigators examined the cancer morbidity and mortality outcome of chlorophenols exposure from fungicides (Demers et al. 2006). The study did not provide evidence of an association between exposure to chlorophenols in fungicides and soft-tissue-sarcoma, lung cancer, sino-nasal cancer, or nasopharyngeal cancer. There were no statistically significant excesses in the specific types of cancers examined (i.e., non-Hodgin's lymphoma, multiple myeloma, and kidney), but when dermal exposure was restricted to fungicides consisting primarily of pentachlorophenol there was a robust dose-response relationship for non-Hodgin's lymphoma, multiple myeloma, and kidney cancer (Demers et al. 2006).

Several other studies examined the possible associations between occupational exposure to chlorophenols and cancer morbidity and mortality (Garabedian et al. 1999; Hoppin et al. 1998; Mirabelli et al. 2000). Moreover, several variables precluded drawing definitive conclusions from these studies: (1) potential misclassification of exposure from use of a post-hoc categorical assignment of subjects to exposure categories, rather than specific measurements of exposure history (e.g., workplace or biomarker monitoring); (2) possibly previous or concurrent chemical exposures which may have contributed to the outcomes that were not adjusted for in the study design or data analysis (e.g., solvents, formaldehyde, chromium, nickel, chlorinated dibenzo-p-dioxins [CDDs], and chlorinated dibenzofurans [CDFs]); and (3) lack of evidence of dose-response relationships in some studies.

## 2.4 MECHANISMS OF ACTION

### 2.4.2 Mechanisms of Toxicity

The potential of chlorophenols to induce conditions of oxidative stress and DNA damage through the formation of reactive metabolites has been evaluated in studies using cell cultures (Bukowska et al. 2003, 2004; Truffin et al. 2003) and isolated DNA (Dai et al. 2005). Results of an in-vitro study in human hepatoma cells indicate that reactive metabolites of 4-chlorophenol may induce or contribute to conditions of oxidative stress (Truffin et al. 2003). Incubation of hepatoma cells (Hep G2 cell line) with 350 μM 4-chlorophenol for 24 to 48 hours significantly reduced the activities of cytochrome P-450 reductase, catalase, and glutathione peroxidase as well as levels of glutathione and ATP. In addition, messenger ribonucleic acid (mRNA) expression of cytochrome P-450 isozymes, CYP 3A7 and CYP 2E1, was significantly increased, with more pronounced effects on CYP 3A7. The authors suggested that the results are consistent with a role for reactive metabolites oxidative stress induced by 4-chlorophenol.

*In-vitro* exposure of human erythrocytes to 2,4-dichlorophenol (Bukowska et al. 2003) and 2,4,5-trichlorophenol (Bukowska et al. 2004) resulted in decreased levels of glutathione and antioxidant enzyme [superoxide dismutase (SOD), catalase] activities, which are indicative of changes associated with oxidative stress. Erythrocytes incubated for 1 hour with 2,4-dichlorophenol at concentrations ranging from 50 to 250 mg/L produced a dose-dependent, statistically significant ($p<0.05$) decrease in SOD activity (maximum decrease of 40% compared to controls) and glutathione levels (maximum decrease of 32% compared to controls), and increases in glutathione peroxidase activity (maximum increase of 71% compared to controls). Erythrocytes incubated for 1 hour with 2,4,5-trichlorophenol at concentrations of 100 and 250 ppm revealed statistically significant ($p<0.05$) decreases in SOD activity (maximum decrease of 41% compared to controls), and catalase activity (maximum decrease of 11% compared to controls), reduced glutathione levels (maximum decrease 25% compared to controls), and an increased percentage of cells with pre-hemolytic changes (maximum increase of 84% of cells with changes compared to 0% in controls) ( Bukowska et al 2004). There were no changes observed for total glutathione levels (reduced plus oxidized glutathione) or glutathione reductase activity.

In *in-vitro* cells were exposed to 100 ppm 2,4,5-trichlorophenol, while adenosine monophosphate (AMP) and adenosine diphosphate (ADP) levels were increased in comparison to controls. Results of these studies are consistent with chloroprophenol-induced free radicals which are known to cause oxidative damage to tissue.

Activation of chlorophenols with peroxidase was found to form reactive intermediates that produced damage to isolated DNA (Dai et al. 2005). Reactive intermediates produced by incubation of 2,4-dichlorophenol, 2,4,5-tri-chlorophenol, or 2,4,6-tri-chlorophenol with horseradish peroxidase formed covalent adducts with deoxyguanosine in isolated calf thymus DNA and in isolated deoxyguanosine. The authors suggested that peroxidase-mediated activation of chlorophenols to phenoxyl radicals may be an important mechanism in chlorophenol-induced toxicity (Dai et al. 2005).

Comparative cytotoxic effects and mediation of cell death through induction of apoptosis was evaluated for 4-chlorophenol, 2,4-dichlorophenol, 2,3,4-trichlorophenol, and pentachlorophenol in fibroblast L929 cells (mouse connective tissue fibroblast cell line) as a function of their octanol-water partition coefficient ($K_{ow}$) and apoptotic response (Chen et al. 2004). Incubation of L929 cells with each of these compounds induced significant dose-and time-dependent reductions in cell growth. The cytotoxicity of chlorophenols as measured by the effective concentration for 50% lethality (EC50) increased with the degree of chlorination and the correlation with $K_{ow}$ was strong at the 24-hour exposure check ($r = 0.99$) but weak after 48 hours ($r = 0.89$). The respective EC50 values for these four chlorophenols at 24 hours were 2.18, 0.83, 0.46, and 0.11, and at 48 hours were 1.18, 0.13, 0.08, and 0.06, while the respective log $K_{ow}$ values were 2.39, 3.21, 4.07, and 5.04. This indicates that $K_{ow}$ is the major factor affecting cell toxicity during the first day of exposure, but additional factors are involved at later times. The results of flow cytometry (for 2,4-dichlorophenol only) and DNA fragmentation analysis (for 4-chlorophenol, 2,4-dichlorophenol, and 2,3,4-trichlorophenol), which is a distinctive feature of apoptosis, revealed dose-and time-dependent effects for these chlorophenol exposures. Observations are consistent with induction of cell death through apoptosis as the mechanism of action for exposure to 4-chlorophenol, 2,4-dichlorophenol, or 2,3,4-trichlorophenol, as opposed to cell necrosis for pentachlorophenol (Chen et al. 2004).

The potential for chlorophenols to produce effects on processes involved in endocrine systems has been evaluated in *in-vitro* studies (Harris et al. 2005; Kim et al. 2005; Okada et al. 2005). Several chlorophenols were evaluated for their potential to inhibit isolated estrogen sulfotransferase (Harris et al. 2005). Sulfonation of estrogen, which results in a pharmacologically inactive substance, is an important process in the attenuation of the steroid-hormone signal in endometrial, mammary, and testicular tissues. 2,3-, 2,4-, 2,5-, and 2,6-Dichlorophenol were potent inhibitors of isolated estrogen sulfotransferase. Other chlorophenols, such as 3,4-and 3,5-dichlorophenols and 4-chlorophenol inhibited estrogen sulfotransferase, but with a lower relative potency. The authors suggested that chlorophenols-induced inhibition of estrogen sulfotransferase could lead to increased intracellular levels of estrogen and thereby potentially alter estrogen-mediated cellular functions. The potential for 2,4-dichlorophenol to potentiate 5α-dihydroxytestosterone action, as assessed by cell proliferation, was evaluated in human prostate cancer cells (lines AR expressed 22v1 and PC3) (Kim et al. 2005). Co-administration of 10 nano-molar (nM) 2, 4 dichlorophenol enhanced the androgenic activity of 5α-dihydroxytestosterone (DHT) by 1.6-fold in

comparison to 10 nM DHT alone. Translocation of the androgen receptor complex to the nucleus was increased in the presence of 2,4-dichlorophenol, suggesting that 2,4-dichlorophenol has the potential to alter androgen-induced transcriptional activity. The potential for 2,4-dichlorophenol to affect thyroid hormone functions was evaluated in an *in-vitro* study using isolated 3,3',5-triiodo-L-thyronine (T3), recombinant protein disulfide isomerase (PDI; an intracellular thyroid hormone binding protein that assists in protein folding), and recombinant nuclear thyroid hormone receptor (Okada et al. 2005). 2,4-Dichlorophenol produced dose-dependent inhibition of PDI activity, PDI-T3 binding, and T3-nuclear thyroid hormone receptor binding. Results indicate that 2,4-dichlorophenol may alter thyroid function through changes in intracellular processing of T3 (Kim et al. 2005).

## 2.5 RELEVANCE TO PUBLIC HEALTH

***Genotoxic Effects.*** Chlorophenols have been tested for genotoxicity in *in-vitro* and *in-vivo* studies. A study evaluating the potential for 2,4-dichlorophenol induction of genotoxic effects following *in-vivo* exposure of male Swiss mice (5/group) yielded positive but not statistically significant) results for chromosomal aberrations and sperm-head abnormalities (Amer and Aly 2001). To assess chromosomal aberrations in bone marrow cells and spermatocytes, mice were administered 2,4 dichlorophenol dissolved in distilled water at 0, 36, 72, or 180 mg/kg by single intraperitoneal injection, and injections were repeated at 36 mg/kg for 3 and 5 consecutive days. Animals were sacrificed 24 hours after administration of the final dose. To assess sperm-head abnormalities, mice were injected daily with 0, 36, 72, or 180 mg/kg 2,4 dichlorophenol in distilled water for 5 consecutive days, and animals were sacrificed 35 days after administration of the first dose. The percentage of chromosomal aberrations in bone marrow cells and spermatocytes was increased ($p \leq 0.05$) compared to controls in mice administered a single dose of 180 mg/kg, but not at lower doses or in mice injected with 36 or 72 mg/kg/day 2,4-dichlorophenol for up to 5 consecutive days. Sperm-head abnormalities were also increased ($p \leq 0.05$) in mice treated with 180 mg/kg/day in comparison to controls, but no increase was observed at lower doses (Amer and Aly, 2001). Male mice exposed by a single oral gavage to 2,5-dichlorophenol at 1,500 mg/kg did not reveal chromosomal damage as assessed by the bone marrow micronucleus assay (Tegethoff et al. 2000).

Results of *in-vitro* studies evaluating the genotoxicity of chlorophenols in mammalian cells are summarized in Table 2-1. In the absence of exogenous metabolic activation (a method previously described by Tsutsui et al. 1984) 4-chlorophenol tested negative for DNA damage in human peripheral lymphocytes (Da Silva et al. 2007), human skin fibroblasts (Ribeiro et al. 2004), mouse lymphoma cells (Ribeiro et al. 2004), and Chinese hamster ovary (CHO) cells (Ribeiro et al. 2005, 2006). Tegethoff et al. (2000) indicated that 2,5-dichlorophenol tested negative for hypoxanthine phosphoribosyl transferase (HPRT) mutation in CHO cells both in the absence and presence of exogenous metabolic activation.

Positive results were observed for 4-chlorophenol-induced chromosome aberrations in Syrian Hamster Embryo (SHE) cells in the presence, but not the absence of exogenous metabolic activation (Hagiwara et al. 2006). By contrast, 4-chlorophenol-induced sister chromatid exchange (SCE) was observed in SHE cells in the absence of exogenous metabolic activation (Miyachi and Tsutsui 2005). The results of these studies, except Miyachi and Tsutsui (2005) suggested that *in-vitro* exposure of mammalian cells to 4-chlorophenol does not produce DNA damage. However, the effect of endogenous metabolic-activation of 4-chlorophenol-induced DNA damage was not reported in most of these studies (See Table 2-1). In addition, 4-chlorophenol-induced chromosomal aberrations and SCE occurred in the absence and presence of exogenous metabolic activation, respectively.

**Table 2-1. Genotoxicity of Chlorophenols *In-Vitro***

| Species (test system) | Chemical | Endpoint | Results | | Reference |
|---|---|---|---|---|---|
| | | | Without metabolic activation | With metabolic activation | |
| Human, peripheral lymphocytes (primary culture) | 4-CP | DNA damage | – | NR | Da Silva et al. 2007 |
| Human, skin fibroblasts (primary culture) | 4-CP | DNA damage | – | NR | Ribeiro et al. 2004 |
| Mouse, lymphoma (L5178Y cell line) | 4-CP | DNA damage | – | NR | Ribeiro et al. 2004 |
| Chinese hamster ovary (K-1 cell line) | 4-CP | DNA damage | – | NR | Ribeiro et al. 2005, 2006 |
| Chinese hamster ovary (K-1-BH4 cell line) | 2,5-DCP | Mutation (HPRT locus mutation) | – | – | Tegethoff et al. 2000 |
| Syrian hamster embryo cells (culture) | 4-CP | Chromosome aberrations | – | + | Hagiwara et al. 2006 |
| Syrian hamster embryo cells (culture) | 4-CP | Chromosome damage (SCE) | + | NR | Miyachi and Tsutsui 2005 |

+ = Positive Result; – = Negative Result; 4-CP = 4-Chlorophenol; 2,5-DCP = 2,5-Dichlorophenol; NR = Not Reported; SCE = Sister Chromatid Exchange; HPRT = Hypoxanthine Phosphoribosyl Transferase; DNA = Deoxyribonucleic acid

## 3. CHEMICAL AND PHYSICAL INFORMATION

No updated data.

## 4. PRODUCTION, IMPORT/EXPORT, USE, AND DISPOSAL

No updated data.

# 5. POTENTIAL FOR HUMAN EXPOSURE

## 5.3 ENVIRONMENTAL FATE

### 5.3.1 Transport and Partitioning

The adsorption potential of 2,4-dichlorophenol, 2,4,6-trichlorophenol, and 2,3,4,5-tetrachlorophenol with an aquatic humic sorbent (HS) was examined as single and mixed solutions at different acidities (pH 3, 5.5, and 7) (Peuravouri et al. 2002). Adsorption increased with increasing chlorine content of the chlorophenols and decreasing pH of the solution. Log $K_{oc}$ values ranged from 2.1 for 2,4-dichlorophenol at pH 7, to 3.30 for 2,3,4,5-tetrachlorophenol at pH 3 for the single solution experiments and from 1.99 for 2,4-dichlorophenol at pH 7 to 3.09 for 2,3,4,5-tetrachlorophenol at pH 3 for the mixed solution experiments. A slightly larger log $K_{oc}$ (2.89) for 2,4-dichlorophenol was measured using sediment samples of varying organic carbon content obtained from the Thermaikos Gulf, Greece (Fytianos et al. 2000).

Bioconcentration factors (BCFs) for 2,4-dichlorophenol in Japanese medaka (*Oryzias latipes*) were determined at five different concentrations (Kondo et al. 2005). The BCF values of 2,4-dichlorophenol ranged from 340±300 at 0.235±0.060 µg /L to 92±27 at 27.3±1.6 µg /L. Generally, BCF values increased as the aqueous concentrations of the chlorophenols decreased.

## 5.5 GENERAL POPULATION AND OCCUPATIONAL EXPOSURE

2,4-Dichlorophenol; 2,4,5-trichlorophenol; and 2,4,6-trichlorophenol were measured in urine samples collected from the U.S. population during the National Health and Nutrition Examination Survey and are reported in the Fourth National Report on Human Exposures to Environmental Chemicals (CDC 2009). The levels are presented in Tables 5-1, and 5-2, and 5-3, respectively.

## Table 5-1 Urinary 2,4-Dichlorophenol

*Metabolite of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D)*

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

| | Survey years | mean (95% conf. interval) | ( 95% confidence interval) 50th | 75th | 90th | 95th | Sample size |
|---|---|---|---|---|---|---|---|
| Total | 03-04 | **1.04** (.895-1.21) | **.900** (.800-1.10) | **2.70** (2.30-3.10) | **8.80** (6.60-11.9) | **21.3** (14.1-29.5) | 2525 |
| | 05-06 | **.945** (.791-1.13) | **.800** (.700-1.00) | **2.00** (1.60-2.40) | **4.90** (3.90-6.30) | **11.9** (7.00-20.4) | 2548 |
| | 07-08 | **.972** (.853-1.11) | **.800** (.700-.900) | **1.80** (1.50-2.30) | **5.10** (3.80-7.60) | **12.9** (9.00-18.1) | 2604 |
| **Age group** | | | | | | | |
| 6-11 years | 03-04 | **1.01** (.796-1.28) | **.800** (.600-1.20) | **2.30** (1.70-3.20) | **7.70** (3.80-20.1) | **23.5** (9.40-31.0) | 314 |
| | 05-06 | **1.01** (.879-1.15) | **.800** (.800-1.10) | **2.00** (1.60-2.30) | **4.90** (3.30-6.60) | **9.80** (6.30-17.6) | 356 |
| | 07-08 | **1.05** (.786-1.39) | **.900** (.700-1.20) | **1.80** (1.20-2.80) | **6.10** (3.00-9.50) | **12.3** (7.70-22.5) | 389 |
| 12-19 years | 03-04 | **1.27** (.971-1.67) | **1.10** (.800-1.50) | **3.40** (2.50-5.00) | **13.6** (6.10-25.5) | **31.5** (14.5-85.0) | 722 |
| | 05-06 | **1.18** (.997-1.39) | **1.00** (.900-1.20) | **2.50** (2.00-3.10) | **5.50** (4.00-8.30) | **13.9** (7.10-33.6) | 702 |
| | 07-08 | **1.20** (.993-1.45) | **1.10** (.900-1.40) | **2.60** (2.10-3.00) | **5.60** (3.10-10.8) | **11.6** (5.70-36.5) | 401 |
| 20 years and older | 03-04 | **1.01** (.874-1.17) | **.900** (.700-1.10) | **2.60** (2.20-3.00) | **8.50** (6.60-10.4) | **19.4** (12.2-27.0) | 1489 |
| | 05-06 | **.907** (.737-1.12) | **.800** (.600-1.00) | **2.00** (1.50-2.40) | **4.90** (3.70-6.40) | **11.1** (6.50-20.9) | 1490 |
| | 07-08 | **.933** (.821-1.06) | **.800** (.700-.900) | **1.70** (1.40-2.20) | **5.00** (3.80-7.60) | **13.4** (9.20-18.1) | 1814 |
| **Gender** | | | | | | | |
| Males | 03-04 | **1.22** (1.02-1.45) | **1.10** (.800-1.50) | **3.00** (2.50-3.50) | **9.40** (6.80-13.9) | **22.7** (13.6-40.9) | 1231 |
| | 05-06 | **1.16** (.973-1.37) | **1.00** (.900-1.20) | **2.40** (2.00-2.80) | **5.50** (4.40-7.90) | **12.9** (7.30-25.3) | 1270 |
| | 07-08 | **1.06** (.944-1.19) | **.900** (.800-1.00) | **1.90** (1.60-2.20) | **5.40** (4.00-8.20) | **13.6** (9.70-18.1) | 1294 |
| Females | 03-04 | **.896** (.754-1.07) | **.800** (.600-.900) | **2.30** (2.00-2.70) | **8.10** (5.70-11.1) | **19.8** (12.0-27.5) | 1294 |
| | 05-06 | **.779** (.637-.954) | **.700** (.500-.800) | **1.50** (1.30-2.10) | **4.30** (2.80-6.20) | **9.40** (5.40-19.6) | 1278 |
| | 07-08 | **.894** (.752-1.06) | **.700** (.600-.800) | **1.80** (1.20-2.50) | **4.80** (3.30-7.70) | **11.9** (7.60-18.6) | 1310 |
| **Race/ethnicity** | | | | | | | |
| Mexican Americans | 03-04 | **1.94** (1.46-2.56) | **1.70** (1.20-2.10) | **4.50** (2.80-9.30) | **26.9** (12.7-52.1) | **66.0** (47.5-84.2) | 617 |
| | 05-06 | **1.97** (1.49-2.59) | **1.60** (1.20-2.10) | **5.00** (3.30-6.60) | **20.9** (8.80-39.7) | **46.5** (21.9-79.5) | 637 |
| | 07-08 | **1.59** (.985-2.57) | **1.20** (.600-2.50) | **4.10** (2.20-9.30) | **13.4** (7.80-29.6) | **38.0** (16.4-74.0) | 531 |
| Non-Hispanic blacks | 03-04 | **2.42** (1.92-3.06) | **2.20** (1.70-2.70) | **7.40** (4.00-9.60) | **20.8** (11.2-38.3) | **49.2** (24.0-69.7) | 636 |
| | 05-06 | **2.45** (1.93-3.12) | **2.10** (1.70-2.40) | **5.20** (3.90-7.40) | **20.3** (10.6-36.9) | **42.6** (21.3-129) | 678 |
| | 07-08 | **1.73** (1.49-2.01) | **1.40** (1.10-1.60) | **3.70** (2.90-4.90) | **17.8** (9.70-25.8) | **37.7** (24.6-56.8) | 597 |
| Non-Hispanic whites | 03-04 | **.837** (.698-1.00) | **.700** (.600-.900) | **2.10** (1.70-2.60) | **6.20** (4.00-8.80) | **13.4** (8.60-22.0) | 1077 |
| | 05-06 | **.734** (.610-.883) | **.700** (.500-.900) | **1.40** (1.20-1.80) | **3.10** (2.70-3.90) | **5.30** (4.30-7.90) | 1038 |
| | 07-08 | **.816** (.732-.909) | **.700** (.600-.800) | **1.50** (1.20-1.80) | **3.00** (2.60-4.40) | **6.40** (4.60-8.80) | 1077 |

Limit of detection (LOD) for survey years 03-04, 05-06, and 07-08 are 0.17, 0.2, and 0.2, respectively.

CDC. 2009. Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport. January 21, 2010.

# Table 5-1 (cont.) Urinary 2,4-Dichlorophenol (creatinine corrected)

*Metabolite of the herbicide 2,4-dichlorophenoxyacetic acid (2,4-D).*

Geometric mean and selected percentiles of urine concentrations (in µg/g of creatinine) for the U.S. population from the National Health and Nutrition Examination Survey.

| | Survey years | mean (95% conf. interval) | ( 95% confidence interval) 50th | 75th | 90th | 95th | Sample size |
|---|---|---|---|---|---|---|---|
| Total | 03-04 | **1.02** (.873-1.18) | **.880** (.770-1.00) | **2.19** (1.84-2.73) | **7.39** (5.00-9.83) | **15.4** (11.1-20.9) | 2522 |
| | 05-06 | **.922** (.798-1.06) | **.750** (.660-.880) | **1.58** (1.33-1.86) | **4.00** (3.00-5.71) | **8.90** (5.98-16.6) | 2548 |
| | 07-08 | **.980** (.869-1.11) | **.790** (.700-.880) | **1.63** (1.36-1.90) | **4.00** (3.14-5.65) | **11.7** (6.85-18.9) | 2604 |
| **Age group** | | | | | | | |
| 6-11 years | 03-04 | **1.23** (.965-1.56) | **1.03** (.750-1.45) | **2.39** (1.82-3.36) | **9.29** (3.98-16.5) | **20.9** (12.9-38.1) | 314 |
| | 05-06 | **1.11** (.950-1.29) | **.970** (.800-1.08) | **1.74** (1.38-2.19) | **4.38** (3.33-7.80) | **10.9** (5.12-23.3) | 356 |
| | 07-08 | **1.29** (1.02-1.64) | **1.06** (.760-1.40) | **2.09** (1.44-3.21) | **4.74** (3.33-9.27) | **11.2** (5.86-24.4) | 389 |
| 12-19 years | 03-04 | **.954** (.725-1.26) | **.790** (.660-1.00) | **2.08** (1.44-3.75) | **8.02** (4.72-12.5) | **14.8** (8.02-40.0) | 720 |
| | 05-06 | **.878** (.765-1.01) | **.700** (.600-.800) | **1.65** (1.22-1.93) | **3.92** (2.90-4.82) | **8.28** (4.82-15.9) | 702 |
| | 07-08 | **.936** (.778-1.13) | **.790** (.640-1.00) | **1.51** (1.14-2.22) | **3.81** (2.38-5.92) | **10.3** (4.28-23.3) | 401 |
| 20 years and older | 03-04 | **1.00** (.863-1.16) | **.870** (.770-1.00) | **2.17** (1.80-2.69) | **7.16** (4.88-9.01) | **15.0** (10.6-20.8) | 1488 |
| | 05-06 | **.909** (.774-1.07) | **.740** (.650-.870) | **1.55** (1.25-1.89) | **4.00** (2.84-6.19) | **8.80** (5.71-16.8) | 1490 |
| | 07-08 | **.958** (.848-1.08) | **.770** (.680-.880) | **1.60** (1.32-1.85) | **3.98** (3.14-5.59) | **12.1** (8.03-18.9) | 1814 |
| **Gender** | | | | | | | |
| Males | 03-04 | **.995** (.850-1.17) | **.900** (.730-1.06) | **2.23** (1.82-2.82) | **6.84** (4.54-9.01) | **13.7** (9.29-21.8) | 1230 |
| | 05-06 | **.927** (.814-1.06) | **.770** (.670-.880) | **1.60** (1.36-1.86) | **4.12** (3.08-5.45) | **8.90** (5.19-16.6) | 1270 |
| | 07-08 | **.893** (.809-.986) | **.730** (.660-.790) | **1.44** (1.29-1.67) | **4.00** (2.97-5.28) | **9.96** (6.70-14.6) | 1294 |
| Females | 03-04 | **1.03** (.845-1.27) | **.870** (.770-1.00) | **2.17** (1.73-2.73) | **8.00** (4.57-12.1) | **17.2** (11.1-23.7) | 1292 |
| | 05-06 | **.916** (.770-1.09) | **.740** (.640-.880) | **1.56** (1.19-1.96) | **3.91** (2.66-6.50) | **8.93** (5.53-23.7) | 1278 |
| | 07-08 | **1.07** (.913-1.26) | **.850** (.730-1.00) | **1.76** (1.43-2.29) | **4.17** (3.13-7.65) | **14.4** (6.79-26.8) | 1310 |
| **Race/ethnicity** | | | | | | | |
| Mexican Americans | 03-04 | **1.76** (1.30-2.38) | **1.33** (1.04-1.74) | **3.85** (2.29-8.81) | **23.8** (10.6-51.6) | **71.4** (30.8-88.8) | 616 |
| | 05-06 | **1.77** (1.38-2.27) | **1.25** (.990-1.73) | **3.79** (2.70-5.35) | **16.6** (6.75-31.8) | **38.1** (23.8-55.3) | 637 |
| | 07-08 | **1.54** (.931-2.54) | **1.18** (.630-2.26) | **3.33** (2.01-5.80) | **13.5** (5.65-30.6) | **33.1** (16.6-55.3) | 531 |
| Non-Hispanic blacks | 03-04 | **1.66** (1.28-2.16) | **1.47** (1.06-1.96) | **4.14** (2.46-7.31) | **14.9** (7.93-20.1) | **22.9** (16.7-45.0) | 635 |
| | 05-06 | **1.72** (1.39-2.14) | **1.32** (1.11-1.56) | **3.28** (2.33-5.35) | **14.9** (7.40-28.1) | **37.0** (15.0-83.4) | 678 |
| | 07-08 | **1.34** (1.14-1.59) | **.990** (.800-1.17) | **2.36** (1.85-3.12) | **13.1** (5.70-23.3) | **33.8** (22.7-41.1) | 597 |
| Non-Hispanic whites | 03-04 | **.864** (.721-1.03) | **.780** (.690-.890) | **1.86** (1.54-2.23) | **5.08** (3.58-8.00) | **10.8** (6.84-18.2) | 1076 |
| | 05-06 | **.772** (.660-.904) | **.670** (.580-.790) | **1.25** (1.07-1.56) | **2.78** (2.11-3.52) | **4.82** (3.33-8.62) | 1038 |
| | 07-08 | **.853** (.766-.950) | **.730** (.660-.810) | **1.36** (1.14-1.67) | **2.97** (2.53-3.33) | **5.29** (3.84-9.38) | 1077 |

Limit of detection (LOD) for survey years 03-04, 05-06, and 07-08 are 0.17, 0.2, and 0.2, respectively.

CDC. 2009. Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport. January 21, 2010.

## Table 5-2 Urinary 2,4,5-Trichlorophenol

*Metabolite of several organochlorine insecticides*

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

| | Survey years | mean (95% conf. interval) | ( 95% confidence interval) 50th | 75th | 90th | 95th | Sample size |
|---|---|---|---|---|---|---|---|
| Total | 03-04 | * | **< LOD** | **.100** (.100-.100) | **.200** (.200-.300) | **.400** (.300-.400) | 2525 |
| | 05-06 | * | **< LOD** | **.100** (.100-.200) | **.300** (.200-.300) | **.400** (.300-.500) | 2548 |
| | 07-08 | * | **< LOD** | **.100** (<LOD-.100) | **.200** (.200-.200) | **.300** (.200-.300) | 2604 |
| **Age group** | | | | | | | |
| 6-11 years | 03-04 | * | **< LOD** | **.100** (.100-.200) | **.200** (.200-.300) | **.300** (.200-.500) | 314 |
| | 05-06 | * | **< LOD** | **.100** (.100-.200) | **.300** (.200-.400) | **.400** (.300-.500) | 356 |
| | 07-08 | * | **< LOD** | **.100** (<LOD-.100) | **.200** (.100-.300) | **.300** (.200-.500) | 389 |
| 12-19 years | 03-04 | * | **< LOD** | **.100** (.100-.200) | **.200** (.200-.300) | **.300** (.200-.500) | 722 |
| | 05-06 | * | **< LOD** | **.100** (.100-.200) | **.300** (.200-.300) | **.400** (.300-.500) | 702 |
| | 07-08 | * | **< LOD** | **.100** (<LOD-.100) | **.200** (.100-.200) | **.200** (.200-.500) | 401 |
| 20 years and older | 03-04 | * | **< LOD** | **.100** (.100-.100) | **.300** (.200-.300) | **.400** (.300-.500) | 1489 |
| | 05-06 | * | **< LOD** | **.100** (.100-.200) | **.300** (.200-.300) | **.400** (.300-.500) | 1490 |
| | 07-08 | * | **< LOD** | **.100** (<LOD-.100) | **.200** (.200-.300) | **.300** (.200-.400) | 1814 |
| **Gender** | | | | | | | |
| Males | 03-04 | * | **< LOD** | **.100** (.100-.100) | **.200** (.200-.300) | **.400** (.300-.400) | 1231 |
| | 05-06 | * | **< LOD** | **.100** (.100-.200) | **.200** (.200-.300) | **.400** (.300-.500) | 1270 |
| | 07-08 | * | **< LOD** | **.100** (<LOD-.100) | **.200** (.200-.200) | **.300** (.200-.300) | 1294 |
| Females | 03-04 | * | **< LOD** | **.100** (.100-.200) | **.200** (.200-.300) | **.400** (.300-.400) | 1294 |
| | 05-06 | * | **< LOD** | **.100** (.100-.200) | **.300** (.200-.400) | **.500** (.300-.500) | 1278 |
| | 07-08 | * | **< LOD** | **.100** (<LOD-.100) | **.200** (.200-.300) | **.300** (.200-.400) | 1310 |
| **Race/ethnicity** | | | | | | | |
| Mexican Americans | 03-04 | * | **< LOD** | **.100** (<LOD-.200) | **.200** (.200-.300) | **.300** (.200-.400) | 617 |
| | 05-06 | * | **< LOD** | **.100** (<LOD-.200) | **.300** (.200-.300) | **.400** (.300-.500) | 637 |
| | 07-08 | * | **< LOD** | **< LOD** | **.200** (.100-.200) | **.200** (.200-.300) | 531 |
| Non-Hispanic blacks | 03-04 | * | **< LOD** | **.200** (.100-.200) | **.300** (.200-.500) | **.400** (.300-.700) | 636 |
| | 05-06 | * | **< LOD** | **.200** (.100-.200) | **.300** (.200-.400) | **.500** (.300-.500) | 678 |
| | 07-08 | * | **< LOD** | **.100** (.100-.200) | **.200** (.200-.300) | **.400** (.300-.500) | 597 |
| Non-Hispanic whites | 03-04 | * | **< LOD** | **.100** (.100-.100) | **.200** (.200-.300) | **.400** (.300-.400) | 1077 |
| | 05-06 | * | **< LOD** | **.100** (.100-.200) | **.300** (.200-.300) | **.400** (.300-.600) | 1038 |
| | 07-08 | * | **< LOD** | **.100** (<LOD-.100) | **.200** (.200-.300) | **.300** (.200-.400) | 1077 |

Limit of detection for Survey years 03-04, 05-06, and 07-08 are 0.1, 0.1, and 0.1 respectively.
< LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
* Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CDC. 2009. Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport. January 21, 2010.

# Table 5-2 (cont.) Urinary 2,4,5-Trichlorophenol (creatinine corrected)

*Metabolite of several organochlorine insecticides*

Geometric mean and selected percentiles of urine concentrations (in µg/g of creatinine) for the U.S. population from the National Health and Nutrition Examination Survey.

| | Survey years | mean (95% conf. interval) | ( 95% confidence interval) 50th | 75th | 90th | 95th | Sample size |
|---|---|---|---|---|---|---|---|
| Total | 03-04 | * | < LOD | .170 (.160-.180) | .280 (.260-.310) | .370 (.330-.420) | 2522 |
| | 05-06 | * | < LOD | .160 (.150-.180) | .290 (.260-.320) | .410 (.360-.450) | 2548 |
| | 07-08 | * | < LOD | .150 (<LOD-.160) | .280 (.230-.320) | .390 (.330-.470) | 2604 |
| **Age group** | | | | | | | |
| 6-11 years | 03-04 | * | < LOD | .180 (.150-.230) | .290 (.250-.320) | .370 (.310-.540) | 314 |
| | 05-06 | * | < LOD | .180 (.140-.200) | .310 (.210-.450) | .450 (.320-.610) | 356 |
| | 07-08 | * | < LOD | .180 (<LOD-.190) | .270 (.210-.390) | .430 (.270-.580) | 389 |
| 12-19 years | 03-04 | * | < LOD | .120 (.100-.140) | .200 (.170-.220) | .240 (.220-.280) | 720 |
| | 05-06 | * | < LOD | .120 (.110-.130) | .210 (.180-.240) | .290 (.240-.330) | 702 |
| | 07-08 | * | < LOD | .100 (<LOD-.120) | .170 (.150-.210) | .250 (.170-.310) | 401 |
| 20 years and older | 03-04 | * | < LOD | .180 (.160-.180) | .290 (.270-.320) | .390 (.350-.470) | 1488 |
| | 05-06 | * | < LOD | .170 (.150-.190) | .300 (.260-.330) | .410 (.370-.470) | 1490 |
| | 07-08 | * | < LOD | .150 (<LOD-.180) | .290 (.230-.350) | .410 (.340-.500) | 1814 |
| **Gender** | | | | | | | |
| Males | 03-04 | * | < LOD | .130 (.110-.150) | .230 (.190-.260) | .320 (.270-.350) | 1230 |
| | 05-06 | * | < LOD | .130 (.120-.140) | .220 (.190-.240) | .310 (.260-.360) | 1270 |
| | 07-08 | * | < LOD | .110 (<LOD-.120) | .190 (.180-.230) | .300 (.230-.340) | 1294 |
| Females | 03-04 | * | < LOD | .200 (.180-.210) | .320 (.290-.350) | .440 (.350-.510) | 1292 |
| | 05-06 | * | < LOD | .210 (.180-.230) | .350 (.300-.410) | .470 (.410-.550) | 1278 |
| | 07-08 | * | < LOD | .190 (<LOD-.230) | .330 (.280-.420) | .470 (.370-.580) | 1310 |
| **Race/ethnicity** | | | | | | | |
| Mexican Americans | 03-04 | * | < LOD | .140 (<LOD-.150) | .240 (.200-.280) | .330 (.280-.460) | 616 |
| | 05-06 | * | < LOD | .140 (<LOD-.160) | .240 (.190-.320) | .350 (.290-.380) | 637 |
| | 07-08 | * | < LOD | < LOD | .210 (.180-.240) | .260 (.230-.320) | 531 |
| Non-Hispanic blacks | 03-04 | * | < LOD | .120 (.100-.150) | .230 (.170-.290) | .310 (.230-.390) | 635 |
| | 05-06 | * | < LOD | .110 (.100-.140) | .210 (.170-.260) | .320 (.260-.360) | 678 |
| | 07-08 | * | < LOD | .120 (.100-.140) | .200 (.170-.250) | .290 (.230-.420) | 597 |
| Non-Hispanic whites | 03-04 | * | < LOD | .180 (.160-.190) | .290 (.260-.320) | .370 (.340-.440) | 1076 |
| | 05-06 | * | < LOD | .180 (.160-.190) | .300 (.270-.350) | .410 (.360-.500) | 1038 |
| | 07-08 | * | < LOD | .160 (<LOD-.190) | .300 (.250-.370) | .440 (.330-.510) | 1077 |

Limit of detection for Survey years 03-04, 05-06, and 07-08 are 0.1, 0.1, and 0.1 respectively.
< LOD means less than the limit of detection for the urine levels not corrected for creatinine.
* Not calculated: proportion of results below limit of detection was too high to provide a valid result.
CDC. 2009. Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport. January 21, 2010.

# Table 5-3 Urinary 2,4,6-Trichlorophenol

*Metabolite of several organochlorine insecticides*

Geometric mean and selected percentiles of urine concentrations (in µg/L) for the U.S. population from the National Health and Nutrition Examination Survey.

| | Survey years | mean (95% conf. interval) | ( 95% confidence interval) 50th | 75th | 90th | 95th | Sample size |
|---|---|---|---|---|---|---|---|
| Total | 03-04 | * | < LOD | .500 (<LOD-.600) | 1.00 (.800-1.20) | 1.40 (1.20-1.80) | 2525 |
| | 05-06 | * | < LOD | .600 (<LOD-.700) | 1.00 (.800-1.20) | 1.40 (1.20-1.80) | 2548 |
| | 07-08 | * | < LOD | < LOD | .800 (.700-.900) | 1.20 (1.00-1.30) | 2604 |
| **Age group** | | | | | | | |
| 6-11 years | 03-04 | * | < LOD | .600 (.500-.700) | 1.10 (.800-1.40) | 1.90 (1.10-3.10) | 314 |
| | 05-06 | * | < LOD | .700 (.600-.900) | 1.30 (1.00-2.30) | 2.70 (1.30-5.40) | 356 |
| | 07-08 | * | < LOD | .600 (<LOD-.700) | 1.10 (.900-1.40) | 1.60 (1.30-2.10) | 389 |
| 12-19 years | 03-04 | * | < LOD | .600 (.500-.800) | 1.20 (.900-1.70) | 1.80 (1.50-2.10) | 722 |
| | 05-06 | * | < LOD | .600 (<LOD-.800) | 1.00 (.800-1.30) | 1.30 (1.20-1.70) | 702 |
| | 07-08 | * | < LOD | .600 (<LOD-.700) | .800 (.700-1.10) | 1.10 (.800-1.70) | 401 |
| 20 years and older | 03-04 | * | < LOD | .500 (<LOD-.600) | 1.00 (.800-1.10) | 1.30 (1.10-1.70) | 1489 |
| | 05-06 | * | < LOD | .600 (<LOD-.700) | 1.00 (.800-1.20) | 1.30 (1.20-1.80) | 1490 |
| | 07-08 | * | < LOD | < LOD | .800 (.700-.900) | 1.10 (.900-1.30) | 1814 |
| **Gender** | | | | | | | |
| Males | 03-04 | * | < LOD | .600 (<LOD-.600) | 1.00 (.800-1.10) | 1.30 (1.10-1.80) | 1231 |
| | 05-06 | * | < LOD | .600 (<LOD-.800) | 1.10 (.900-1.30) | 1.60 (1.20-2.00) | 1270 |
| | 07-08 | * | < LOD | .500 (<LOD-.600) | .800 (.700-1.00) | 1.20 (1.10-1.40) | 1294 |
| Females | 03-04 | * | < LOD | .500 (<LOD-.600) | 1.10 (.900-1.20) | 1.40 (1.10-2.00) | 1294 |
| | 05-06 | * | < LOD | .500 (<LOD-.600) | .900 (.800-1.20) | 1.30 (1.10-1.70) | 1278 |
| | 07-08 | * | < LOD | < LOD | .800 (.700-.900) | 1.10 (.900-1.40) | 1310 |
| **Race/ethnicity** | | | | | | | |
| Mexican Americans | 03-04 | * | < LOD | .700 (.600-.800) | 1.20 (1.10-1.60) | 1.80 (1.30-2.00) | 617 |
| | 05-06 | * | < LOD | .600 (.500-.700) | 1.00 (.800-1.20) | 1.30 (1.20-1.70) | 637 |
| | 07-08 | * | < LOD | < LOD | .700 (.700-.900) | 1.00 (.900-1.20) | 531 |
| Non-Hispanic blacks | 03-04 | * | < LOD | .900 (.700-1.00) | 1.40 (1.10-1.90) | 2.00 (1.50-2.70) | 636 |
| | 05-06 | * | < LOD | .800 (.700-1.10) | 1.50 (1.20-1.90) | 2.20 (1.60-3.30) | 678 |
| | 07-08 | * | < LOD | .600 (.500-.600) | 1.00 (.900-1.10) | 1.30 (1.10-1.60) | 597 |
| Non-Hispanic whites | 03-04 | * | < LOD | < LOD | .800 (.700-1.00) | 1.20 (1.00-1.50) | 1077 |
| | 05-06 | * | < LOD | .500 (<LOD-.700) | .900 (.700-1.30) | 1.30 (1.10-1.80) | 1038 |
| | 07-08 | * | < LOD | < LOD | .800 (.700-.900) | 1.20 (.900-1.40) | 1077 |

Limit of detection (LOD, ) for Survey years 03-04, 05-06, and 07-08 are 0.5, 0.5, and 0.5 respectively.
< LOD means less than the limit of detection, which may vary for some chemicals by year and by individual sample.
* Not calculated: proportion of results below limit of detection was too high to provide a valid result.

CDC. 2009. Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport. January 21, 2010.

## Table 5-3 (cont.) Urinary 2,4,6-Trichlorophenol (creatinine corrected)

*Metabolite of several organochlorine insecticides*

Geometric mean and selected percentiles of urine concentrations (in µg/g of creatinine) for the U.S. population from the National Health and Nutrition Examination Survey.

| | Survey years | mean (95% conf. interval) | ( 95% confidence interval) 50th | 75th | 90th | 95th | Sample size |
|---|---|---|---|---|---|---|---|
| Total | 03-04 | * | < LOD | .710 (<LOD-.780) | 1.25 (1.17-1.35) | 1.75 (1.59-2.06) | 2522 |
| | 05-06 | * | < LOD | .720 (<LOD-.760) | 1.27 (1.17-1.38) | 1.75 (1.59-1.94) | 2548 |
| | 07-08 | * | < LOD | < LOD | 1.25 (1.06-1.42) | 1.75 (1.52-2.19) | 2604 |
| **Age group** | | | | | | | |
| 6-11 years | 03-04 | * | < LOD | .920 (.850-1.13) | 1.59 (1.22-1.91) | 2.11 (1.46-4.55) | 314 |
| | 05-06 | * | < LOD | .880 (.740-1.06) | 1.59 (1.21-2.06) | 2.50 (1.61-5.20) | 356 |
| | 07-08 | * | < LOD | .900 (<LOD-.930) | 1.46 (1.14-1.65) | 2.33 (1.52-2.92) | 389 |
| 12-19 years | 03-04 | * | < LOD | .580 (.510-.660) | .970 (.830-1.10) | 1.21 (1.09-1.49) | 720 |
| | 05-06 | * | < LOD | .550 (<LOD-.630) | .970 (.690-1.17) | 1.40 (1.08-1.59) | 702 |
| | 07-08 | * | < LOD | .550 (<LOD-.610) | .830 (.730-1.03) | 1.30 (.950-1.48) | 401 |
| 20 years and older | 03-04 | * | < LOD | .710 (<LOD-.770) | 1.25 (1.17-1.35) | 1.75 (1.59-2.00) | 1488 |
| | 05-06 | * | < LOD | .730 (<LOD-.780) | 1.30 (1.17-1.40) | 1.75 (1.57-2.06) | 1490 |
| | 07-08 | * | < LOD | < LOD | 1.30 (1.06-1.46) | 1.84 (1.52-2.33) | 1814 |
| **Gender** | | | | | | | |
| Males | 03-04 | * | < LOD | .560 (<LOD-.600) | .920 (.820-1.10) | 1.30 (1.17-1.46) | 1230 |
| | 05-06 | * | < LOD | .600 (<LOD-.650) | 1.00 (.850-1.13) | 1.43 (1.25-1.59) | 1270 |
| | 07-08 | * | < LOD | .530 (<LOD-.600) | .930 (.830-1.09) | 1.46 (1.17-1.59) | 1294 |
| Females | 03-04 | * | < LOD | .900 (<LOD-.960) | 1.59 (1.35-1.75) | 2.19 (1.75-2.63) | 1292 |
| | 05-06 | * | < LOD | .850 (<LOD-.970) | 1.46 (1.30-1.67) | 2.06 (1.67-2.50) | 1278 |
| | 07-08 | * | < LOD | < LOD | 1.46 (1.22-1.75) | 2.19 (1.67-2.50) | 1310 |
| **Race/ethnicity** | | | | | | | |
| Mexican Americans | 03-04 | * | < LOD | .760 (.600-.900) | 1.15 (.970-1.38) | 1.59 (1.18-2.42) | 616 |
| | 05-06 | * | < LOD | .650 (.570-.700) | 1.03 (.860-1.19) | 1.46 (1.11-1.94) | 637 |
| | 07-08 | * | < LOD | < LOD | 1.03 (.900-1.13) | 1.33 (1.13-1.52) | 531 |
| Non-Hispanic blacks | 03-04 | * | < LOD | .600 (.560-.640) | .950 (.800-1.10) | 1.34 (1.06-1.67) | 635 |
| | 05-06 | * | < LOD | .630 (.540-.740) | 1.03 (.830-1.49) | 1.59 (1.13-2.07) | 678 |
| | 07-08 | * | < LOD | .520 (.470-.620) | 1.00 (.830-1.13) | 1.40 (1.13-1.52) | 597 |
| Non-Hispanic whites | 03-04 | * | < LOD | < LOD | 1.30 (1.17-1.46) | 1.75 (1.59-2.11) | 1076 |
| | 05-06 | * | < LOD | .760 (<LOD-.830) | 1.35 (1.25-1.50) | 1.79 (1.60-2.06) | 1038 |
| | 07-08 | * | < LOD | < LOD | 1.35 (1.13-1.52) | 1.84 (1.52-2.50) | 1077 |

Limit of detection (LOD, ) for Survey years 03-04, 05-06, and 07-08 are 0.5, 0.5, and 0.5 respectively.
< LOD means less than the limit of detection for the urine levels not corrected for creatinine.
* Not calculated: proportion of results below limit of detection was too high to provide a valid result.
CDC. 2009. Fourth national report on human exposure to environmental chemicals. Centers for Disease Control and Prevention. http://www.cdc.gov/exposurereport. January 21, 2010

# 6. ANALYTICAL METHODS

## 6.2 ENVIRONMENTAL SAMPLES

Analysis of chlorophenols in aqueous samples using a solid-phase micro-extraction technique followed by analysis with gas chromatography-mass spectrometry (GC-MS) was described by Bagheri et al. (2008). In order to improve separation efficiency, all compounds were derivatized using acetic anhydride under alkaline conditions prior to extraction, which used a sol-gel-based amino-functionalized fiber. The detection limits of the method under optimized conditions were in the range of 0.02 to 0.05 nanograms/milliliter (ng/ml) (20 to50 ng/l). Ho et al. (2008) also described a solid-phase micro-extraction technique followed by analysis using GC-MS for the measurement of chlorophenols in aqueous samples. Using purge-assisted headspace solid-phase micro-extraction, derivatization from the matrices to the headspace was avoided and detection limits of 0.1to 0.4 picrograms/milliliter (pg/ml) (0.1to 0.4 ng/l) were achieved.

An analytical method for the analysis of 19 different chlorophenols in various matrices was discussed by Diserens (2001). Liquid extraction using a solution of sodium carbonate in the presence of hexane and acetic anhydride followed by GC-MS was employed for quantification. Detection limits of <20 micrograms/kilogram (µg/kg) were achieved for wood, cardboard, and paper, while detection limits of <2 µg/kg for chlorophenols were achieved for fruit samples.

Analysis of chlorophenols in contaminated soil samples was studied using subcritical water (water heated above the normal boiling point and maintained under pressure to preserve the liquid state) combined with solid-phase microextraction followed by GC-MS (Wennrich et al 2000). Detection limits for various chlorophenols were generally in the range of 1 to 9 µg/kg.

# 7. REGULATIONS AND ADVISORIES

## Table 7-1. Regulations and Guidelines Applicable to Chlorophenols

| Agency | Description | Information | Reference |
|---|---|---|---|
| INTERNATIONAL | | | |
| Guidelines: | | | |
| WHO | Drinking water quality guidelines | | WHO 2006 |
| | 2,4,6-Trichlorophenol | 0.2 mg/L[a,b] | |
| NATIONAL | | | |
| Regulations and Guidelines: | | | |
| a. Water | | | |
| EPA | Drinking water standards and health advisories | | EPA 2011 |
| | 1-Day health advisory for a 10-kg child | | |
| | 2,4,6-Trichlorophenol | 0.03 mg/l | |
| | 10-Day health advisory for a 10-kg child | | |
| | 2,4,6-Trichlorophenol | 0.03 mg/l | |
| | DWEL | | |
| | 2,4,6-Trichlorophenol | 0.01 mg/l | |
| | Lifetime | | |
| | 2,4,6-Trichlorophenol | No | |

[a]For substances that are considered to be carcinogenic, the guideline value is the concentration in drinking water associated with an upper-bound excess lifetime cancer risk of $10^{-5}$ (one additional cancer per 100,000 of the population ingesting drinking water containing the substance at the guideline value for 70 years). Concentrations associated with upper-bound estimated excess lifetime cancer risks of $10^{-4}$ and $10^{-6}$ can be calculated by multiplying and dividing, respectively, the guideline value by 10 (WHO 2006).
[b]Concentrations of the substance at or below the health-based guideline value may affect the appearance, taste, or odor of the water, leading to consumer complaints (WHO 2006).

DWEL = drinking water equivalent level; EPA = Environmental Protection Agency; WHO = World Health Organization

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