

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY  
DEPARTMENT OF PESTICIDE REGULATION  
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA  
PCP (PENTACHLOROPHENOL)

SB 950 # 114, Tolerance # 50221, Chemical Code #465

Original version: January 5, 1987

Updated 7/7/87, 10/4/88, 6/13/89, 3/8/94, 7/28/94, 9/7/94, 1/23/95, 6/14/95, 5/6/96, 3/18/97  
and 2/26/98

I. DATA GAP STATUS

Chronic, rat:	No data gap, no adverse effects
Chronic, dog:	No data gap, possible adverse effects
Oncogenicity, rat:	No data gap, possible adverse effects
Oncogenicity, mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effects
Teratogenicity, rat:	No data gap, possible adverse effects
Teratogenicity, rabbit:	No data gap, no adverse effects
Gene mutation:	No data gap, no adverse effects
Chromosome effects:	No data gap, possible adverse effects
DNA damage:	No data gap, possible adverse effects
Neurotoxicity:	Not required at this time

---

**Note, Toxicology one-liners are attached**

In the document/record number citations below:

\*\* indicates acceptable study

**Bold face** indicates possible adverse effect

This update of the Summary of Toxicological Data has considered all relevant PCP data indexed by DPR up to 2/09/98, i.e. all records through No. 159038 (Document No. 50221-226). C. Aldous, Feb. 9, 1998.

NOTE: There are two registered salts of PCP; sodium (Chemical No. 50788), and potassium (Chemical No. 50789). These are grouped for purposes of data submission with the "lead chemical", PCP. As of 5/6/96, there were no SB-950 studies submitted under these two chemical numbers.

**NOTE:** EPA has phased down the allowable levels of particularly hexachlorodibenzo dioxins (HxCDDs) in technical PCP. The acceptable levels of HxCDDs are currently being monitored and reduced in steps, as indicated in the document issued by John A. Moore of EPA's Office of Pesticides and Toxic Substances [OPP-30000/28M; FRL 52 FR-140; DPR Doc. # 50221-034], entitled "Pentachlorophenol; amendment of notice of intent to cancel registration". The new technicals, being purer than the technicals employed in previous studies, may differ from previous technicals in toxicological risk. Aldous, 10/4/88.

**NOTE:** EPA had discussed oncogenic risk of PCP mainly in terms of hexachlorodibenzodioxins (HxCDDs). EPA used the August 1980 Technical Report of an NCI study (DHHS Publication No. (NIH) 80-1754) as the basis for HxCDD-associated oncogenic risk evaluation. Significant weaknesses of the NCI study were discussed in 50221-028:035669 and :035670 ("Audit of NCI bioassay on orally administered HCDD to rats and mice"). EPA has considered this audit in review of the NCI data, and has issued the new human risk estimate based on their own re-evaluation of the data (see the P/D 4 for the wood preservative pesticides in 50436-008:002601, pp. 10-16). Not all data indicate that HxCDDs are the whole or chief consideration in hazard evaluation of PCP (see for example rat teratogenicity study 50221-033:54867, below). Data produced from studies of technical PCP are used by DPR in preference to surrogate data based on the amounts of HxCDDs in technical PCP. As of 1998, all major study types are represented by acceptable data on pentachlorophenol, and all except for mutagenicity categories have studies using modern technical grade pentachlorophenol. Aldous, 10/4/88, revised 2/26/98.

## II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

### COMBINED

**\*\*50221-266 159038** Hejtmancik, M. and P. J. Kurtz (Principal Investigators), "NTP technical report on the toxicology and carcinogenesis studies of pentachlorophenol (CAS No. 87-86-5) in F344/N rats (feed studies)", Batelle Columbus Laboratories (conducted study for NIH), (board draft: scheduled peer review date was 9-10 Dec., 1997). Laboratory Study # NTP TR 483. Comparatively pure PCP (approx. 99% a.i.) was administered in diet to 50 F344/N rats/sex/group at 0, 200, 400, 600, or 1000 ppm. Corresponding daily dosages were reported to be 0, 10, 20, 30, and 60 mg/kg/day. Dosing of the 1000 ppm group was stopped after 52 weeks; those rats being placed thereafter on control diet. An additional 10/sex were dosed with 0 or 1000 ppm for an interim evaluation (limited clinical chemistry and histopathology) after 7 months. This study is different from a guideline "combined" rat study in several ways, such as limited clinical chemistry and no hematology nor ophthalmology. Apparent NOEL = 200 ppm (modest body weight decrements). Investigators noted that squamous cell carcinoma (nasal area) and malignant mesotheliomas were elevated in 1000 ppm stop-dose males (statistically significant and/or outside historical control range); and considered these findings as indicating "some evidence of carcinogenic activity". Keratoacanthomas in skin of 1000 ppm stop-dose males were also significantly elevated over controls. Neoplastic effects were not indicated at 600 ppm or lower in males, nor in females at any dose level. Study is **acceptable** to address oncogenicity data requirements. Further, this study plus other studies previously submitted address rat chronic toxicity study requirements. The increased incidences of the above tumors in 1000 ppm males indicate **possible adverse effects**, particularly the nasal tumors. Aldous, 2/26/98.

The NTP Technical Reports Review Subcommittee has met to review the data of the above study (see [http://ntp-server.niehs.nih.gov/htdocs/Liason/PR\\_Actions\\_12\\_97.html](http://ntp-server.niehs.nih.gov/htdocs/Liason/PR_Actions_12_97.html)). The report, entitled "Actions on Draft Technical Reports By NTP Technical Reports Review Subcommittee, December 9-10, 1997" states as follows:

"The Subcommittee recommended unanimously (8 votes) that the conclusions for rats be split with the conclusions for the 2-year exposure study at 200, 400, or 600 ppm being **no evidence of carcinogenic activity** in male and female rats, with the conclusions for the 1-year stop-exposure study at 1000 ppm being **some evidence of carcinogenic activity\*** in male rats and **no evidence of carcinogenic activity** in female rats."

\*The "Conclusions" section of the updated draft refers to . . . "*some evidence of carcinogenic activity* of pentachlorophenol in the 1-year stop-exposure study at 1000 ppm in male F344/N rats based on increased incidences of mesothelioma and nasal squamous cell carcinoma".  
(See <http://ntp-server.niehs.nih.gov/htdocs/LT-studies/tr483.html>).

50221-045 127238 Interim report for 50221-266 159038, above

### CHRONIC, RAT

50221-032 054848 "Results of a toxicological evaluation of pentachlorophenol sample XD-8108.00L administered to rats by the dietary route on a chronic basis". Toxicology Research Lab, Dow (Midland); 8/24/76. PCP was "representative commercial product" (Dowicide EC-7), 90.4% purity (also 1 ppm hexachlorodibenzodioxins, 3.4 ppm hexachlorodibenzofuran). 0, 1, 3, 10, and 30 mg/kg/day for 22 mos (M) or 24 mos (F). (27 rats/group initially). Apparent NOEL = 3 mg/kg/day (brown granular pigmentation in centrilobular hepatocytes and associated reticulocytes, similar pigmentation in tubular epithelial cells of kidneys, both in females). Female body weight gain reduced and additional liver and kidney effects at 30 mg/kg/day. No oncogenic response noted. **Not acceptable nor upgradeable**: too few animals on study, too few males surviving, blood chemistry/hematology inadequate in items measured, frequency of measurements, and numbers of animals. Study inadequate for either chronic or oncogenicity data requirements. (C. Aldous, 6/30/87; study re-examined but no additional worksheets generated in preparation of rebuttal document, 10/4/88). See subchronic study one-liners below regarding studies submitted in support of the chronic study data requirement. These were discussed in CDFA Rebuttal Response of 6/13/89 (C. Aldous).

50221-038 073639 Schwetz, B. A., et al., "Results of two-year toxicity and reproduction studies on pentachlorophenol in rats", B. A. Schwetz et al. Chapter in a volume entitled Pentachlorophenol: Chemistry, Pharmacology, and Environmental Toxicology, K. R. Rao, Ed., New York, 1978. [Dow Chemical U.S.A., Midland, MI]. Published summary of 032:054848 and 033:054870. No worksheet needed. C. Aldous, 6/13/89.

50221-051 136845 Noted as exact duplicate of 073639 above.

038 073637 "Chlorinated dibenzodioxins and pentachlorophenol", R. L. Johnson, et al., Environmental Health Perspectives, Issue No. 5, September 1973. Chemical Biology Research Laboratory, Dow Chemical Co., Midland, MI. Three parallel 90-day rat feeding studies were conducted in Sprague-Dawley rats (Spartan strain). Details such as sex/sexes and numbers/group were not specified, but all three studies are presumed by DPR to be similar in design to study 038:073636 [which is undoubtedly the "improved PCP" material study included in this report]. Test articles in the three studies were [pre-1970's grade] commercial PCP, "chemically pure PCP", and "improved PCP" (which is, by inference to study 038:073636, comparable to Dovicide EC-7). Findings in the latter two studies were considered comparable: liver weight increases at 10 and 30 mg/kg/day, kidney weight increases at 30 mg/kg/day only, NOEL therefore = 3 mg/kg/day. In contrast, the old commercial PCP caused liver and kidney weight increases at 3 mg/kg/day and above, focal hepatocellular degeneration and necrosis at 30 mg/kg/day, elevated serum alkaline phosphatase at all three dosages, hematological depression at 30 mg/kg/day, a positive rabbit ear bioassay (for chloracne), and a positive chick edema bioassay. Report is **unacceptable** (no individual data, minimal description of methods: deficiencies observed in study 038:073636 are presumed to apply to this report also). Useful qualitative data were provided. C. Aldous, 6/9/89.

038 (no Record No.) "Attachment 8" in this volume. "The effect of technical and 99% pure pentachlorophenol on the rat liver. Light microscopy and ultrastructure." Kimbrough and Linder, Toxicol. Appl. Pharmacol. 33:131-132 (1975). A one-paragraph abstract. Groups of ten male rats were fed 1000 ppm pure or technical pentachlorophenol for 3 mo and compared to two groups of ten controls each. Liver enlargement was found in all treated rats. Treatment effects in both treatment groups included increased smooth endoplasmic reticulum, increased lipid vacuoles, and atypical mitochondria. Additional findings noted in rats fed technical PCP included "foamy cytoplasm or pronounced vacuolation of the hepatocytes, inclusions, single hepatocellular necrosis, slight interstitial vacuolation of the hepatocytes, slight interstitial fibrosis, and a prominent brown pigment in macrophages and Kupffer cells". When technical PCP was fed at levels of 500, 100, 20 and 0 ppm for 8 months, the 500 ppm group had enlarged livers at necropsy. Thus the apparent LEL was about 25 mg/kg/day, and the apparent NOEL was about 5 mg/kg/day. (Not acceptable study, no DPR worksheet). C. Aldous, 6/9/89.

038 073638 "Effects of pentachlorophenol on hepatic drug-metabolizing enzymes and porphyria related to contamination with chlorinated dibenzo-p-dioxins and dibenzofurans", J. Goldstein et al., Biochem. Pharmacol. 26:1549-1557, (1977). [Pre-1970's grade] technical and "pure grade" PCP were administered in diets of female Sherman rats (6/group) for 8 months, at dosages of 0, 20, 100, and 500 ppm. Body weight gain was reduced at 500 ppm for "pure" and "technical". Marked enzyme induction (aryl hydrocarbon hydroxylase, glucuronyl transferase) was dose-related in "technical" at all dosages, and porphyria was observed in 100 and 500 ppm "technical" groups. The apparent NOEL for "pure grade" PCP was 100 ppm (based on reduced body weight gain, modest increase in glucuronyl transferase activity, and "darkened" livers). There was apparently no systematic microscopic examination of tissues. (Not acceptable study, not upgradeable: no DPR worksheet). C. Aldous, 6/12/89.

50221-044 127004 A small package submitted by Vulcan Chemicals to Donald G. Barnes of the U.S. EPA Science Advisory Board respecting "Carcinogen" risk assessment of Pentachlorophenol. There are no new data, and the document concerns risk characterization. No DPR worksheet is needed. Aldous, 3/8/94.

## CHRONIC, DOG

**\*\*50221-053 146512** Mecler, F. J., "Fifty-two week repeated dose chronic oral study of pentachlorophenol administered via capsule to dogs", TSI Mason Laboratories, Study No. 2-J31, 3/27/96. Four beagles/sex/group received pentachlorophenol (90.9%) daily by capsule at 0, 1.5, 3.5, or 6.5 mg/kg/day for 1 yr. No NOEL was identified in this study. Liver changes observed at all dose levels included elevated liver weights, associated with gross discoloration and microscopic findings of brown, granular cytoplasmic pigment accumulation; and chronic inflammation (lymphocytic aggregations in the vicinity of portal and hepatic venules). Increases in alkaline phosphatase at all dose levels was probably related to liver dysfunction. Stomach mucosa was affected at all dose levels by lymphocytic inflammatory foci. Consistent histopathologic changes at 3.5 to 6.5 mg/kg/day included increased degree and/or incidence of hepatocellular cytoplasmic vacuolation. Elevated serum cholesterol levels and ALT activity elevations at these dose levels were evidently liver-related. These two higher dose groups showed signs of anemia (sporadic clinical signs of pale mucous membranes; dose-related decrements in RBC counts, Hb, and HCT; and splenic extramedullary hematopoiesis). One high dose dog per sex died of chronic exposure: each had signs of vomiting, inappetence, dehydration, and jaundice prior to death. Deaths were judged to be due to liver failure. High dose survivors tended to have appreciable body weight decrements, as well as remarkable increases in cholesterol and in liver "leakage enzymes". Study is **acceptable**. The 1996 review indicated that the study indicated "**possible adverse effects**". The original basis for this classification was due to a lack of a NOEL for several of the above findings. Data were re-examined (see review for Record No. 148859, below), and 3.5 mg/kg/day was determined as a NOAEL for chronic effects, based on liver necrosis and on mortalities attributed to liver disfunction. Aldous, 5/6/96 and 3/17/97.

50221-055 148859 Bernard, B. K., "Petition for reconsideration - Review Document Record No. 146512", Addendum to Document # 50221-053, Record #146512. Letter was dated 8/13/96. This submission was sent in response to the DPR data review conclusions on the cited dog chronic study. That review had concluded that the study indicated a "possible adverse effect", based on the lack of a NOEL and the relatively low LEL obtained in the study. This submission emphasized the need to separate chronic effects from acute effects and physiological adaptive responses. The data were re-examined by DPR in order to provide a chronic NOAEL, with the following results. The high dose elicited 2 deaths attributed to liver toxicity and hepatocellular necrosis in 3/6 high dose survivors. This is a **possible adverse effect**, and it constitutes a LOAEL for chronic toxicity. Other findings such as GI tract inflammatory foci and bleeding and anemia probably resulting therefrom were not progressive over time, and appear to represent persistent acute effects. Thus the chronic NOAEL is 3.5 mg/kg/day. No NOEL was obtained for acute/subacute toxicity nor for adaptive changes (hepatocellular vacuolization and pigment accumulation). The latter changes were either evidently reversible or not associated with functional impairment. Aldous, 3/17/97.

## SUBCHRONIC, DOG

**50221-056 151957** [no report author given for this draft report: Study Director was M. R. Osheroff], "Ninety day repeated dose oral toxicity study of pentachlorophenol administered via capsule to dogs", TSI Mason Laboratories, draft issue date: 11/8/96 (in-life phase was 6/22/93-9/21/93). Beagles, 4/sex/group, were dosed daily by gelatin capsule with 0, 0.7, 3, or 7 mg/kg/day pentachlorophenol (88.9%) for 90 days in a standard subchronic study. The high

dose was initially 10 mg/kg/day, but this proved excessive and was reduced to 7 mg/kg/day from day 15 onward. This was a range-finding study for the subsequent chronic study (DPR Record No. 146512). No NOEL was determined in this study. Findings at the LDT included hepatocellular cytoplasmic vacuolization (1 female), adrenal cortical cytoplasmic vacuolization (1 male), and lymphoid hyperplasia of the stomach mucosa (1 male). A single incidence of hepatocellular single cell necrosis at 7 mg/kg/day, consistent with findings at a similar dose level in the dog chronic study, is a **possible adverse effect**. The NOAEL is 3 mg/kg/day for this study. High dose findings in this study included marked body weight decrements, increased liver weights, hepatocellular hypertrophy and cytoplasmic vacuolization, and plausibly liver-related elevations in serum cholesterol, alanine aminotransferase, and alkaline phosphatase. Many of these findings in liver and adrenal cortex were also observed at 3 mg/kg/day. Common findings at 3 and 7 mg/kg/day included presumed contact surface injuries, such as congestion, inflammation, and hemorrhages in stomach and intestinal tract. SB-950 does not require a "complete and acceptable" dog subchronic study, and this report is satisfactory as a supplementary study in support of the dog chronic study. C. Aldous, 3/13/97.

### ONCOGENICITY, RAT

As yet there are no acceptable studies, however see interim report for a rat oncogenicity study (Document No. 50221-045, Record No. 127238). A 1-liner for that interim report is found under "Chronic, Rat", above (Aldous, 3/8/94).

### ONCOGENICITY, MOUSE

**\*\*50221-030 067571** "NTP technical report on the toxicology and carcinogenesis studies of pentachlorophenol (CAS No. 87-86-5) in B6C3F1 mice (Feed studies)" Battelle Columbus Laboratories, (This draft is not finalized). Scheduled date of Peer Review by NTP Board of Scientific Counselors was 4/18/88. Two test substances: a composite lot of technical PCP (90.4% purity, Lot No. METABOLITE-528) representative of technical used historically; and Dowicide EC-7 (91% purity, Lot 05217D). [Hereafter the two test articles are called "technical." or "EC-7"]. EC-7 had more tetrachlorophenol than technical (9.4 to 3.8%), however technical typically contained much higher levels of the various dibenzodioxins and dibenzofurans. EC-7 was selected to represent products likely to be produced commercially in response to EPA's rigorous standards for controlling dibenzodioxins and dibenzofurans. Two control groups had 35/sex/group of B6C3F1 mice, and there were 50/sex/group of (1) technical at 100 or 200 ppm or (2) EC-7 at 100, 200, or 600 ppm. Results: Combined incidence of **hepatocellular adenomas plus carcinomas** in controls through increasing dosages were: 7/32, 26/47, and 37/48 for technical males; 3/33, 9/49, and 9/50 for technical females; 6/35, 19/48, 21/48, and 34/49 for EC-7 males; and 1/34, 4/50, 6/49, and 31/48 for EC-7 females. Major accompanying signs of liver toxicity observed down to the lowest dosages of technical and EC-7 included: cytomegaly, associated with marked pleomorphism; acute diffuse necrosis of individual hepatocytes; inflammatory responses; and multifocal pigmentation. Other liver findings were dose-related but not as universal, and generally were observed at all dosages for either sex with either test article. These included bile duct hyperplasia, foci of hepatocytes with finely vacuolated cytoplasm, and proliferation of hematopoietic cells. **Pheochromocytomas** were typically benign, bilateral lesions. Incidence was clearly treatment-related, and was expressed primarily in males. Incidence of pheochromocytomas in controls through increasing dosages was: 0/31, 10/45, and 23/45 for technical males; 0/33, 4/48, and 2/49 for technical

females; 1/34, 4/48, 21/48, and 45/49 for EC-7 males; and 0/35, 2/49, 2/46, and 38/49 for EC-7 females. **Hemangiosarcomas** were observed in females with incidence in controls through increasing dosage groups of 0/35, 3/50, and 6/50 for technical and 0/35, 1/50, 3/50, and 8/49 for EC-7. In addition, one high dose EC-7 female had a hemangioma. These above tumors and liver lesions were the major findings, and constitute **possible adverse effects** requiring risk assessment. **Acceptable.** C. Aldous, 9/29/88.

50221-040 075632 Final report for NTP mouse study reviewed as Record No. 067571, above. The only noted difference in the final report is an additional table for historical incidence for hepatocellular tumors in females (p. 159). Since the original CDFA review found the draft report acceptable for regulatory purposes, there will be no new worksheet for the final draft. Aldous, 3/2/94.

50221-037 067128 (Supplementary information to 030:067571, an NTP mouse oncogenicity study). Date of cover letter associated with volume: 4/1/88. This record has two major parts. Section A affects interpretation of data for risk assessment, and is entitled: "Pentachlorophenol carcinogenicity: Comparison of NTP bioassay findings for pentachlorophenol vs. hexachlorodioxin findings". Balance of volume, sections B through E, are "final" revisions of the NTP report. Sections B and C are results of various statistical tests on a producer's composite "technical" PCP and Dowicide "EC-7" PCP findings, respectively, from the final report. Sections D and E are individual histopathology data from the report for the respective test articles. Section A of this volume is an analysis of data of mouse oncogenicity study 030:067571 and a comparison to previously obtained data on hexachlorodioxin (HxCDD). The most important conclusion of this section is that EPA should allow these new data on PCP's to supersede the surrogate data (based on hexachlorodibenzodioxin studies, which also found hepatocellular tumor effects, but which did not find other tumor types elicited by the two PCP test articles in record 030:067571). DPR **uses data derived from the test articles in preference to surrogate data.** New data tables of histopathology data in Sections D and E are consistent with tables in Vol. 30, which was originally reviewed. No change in status of study. New analysis in Section A and statistical evaluations in Sections B and C are potentially useful for risk evaluation. C. Aldous, 9/28/88.

## REPRODUCTION, RAT

**NOTE:** The recent reproduction study below replaces a 1974 study, which had been classified as unacceptable due to many deviations from current guidelines. The new study used much larger group sizes than the older study, and provides a perspective on the comparative reproductive and parental aspects of toxicity of PCP. Primary toxicity appears to affect the parental rats, and no adverse reproductive effects are indicated. Since the recent study meets guidelines, it is recommended that this study be used for evaluation of estimated NOEL's, rather than to rely on apparent NOEL's from the older study. Aldous, 2/9/98.

\*\*50221-265 159037 Hoberman, A. M., "Oral (gavage) two-generation (one litter per generation) reproduction study of pentachlorophenol in rats", Argus Research Laboratories, Inc., 12/23/97. Laboratory Project ID: Argus 2119-006. Thirty CrI:CD®BR VAF/Plus® per group were dosed with 0, 10, 30, or 60 mg/kg/day pentachlorophenol daily by gavage in a reproduction study. These additional parameters were evaluated: estrous cycling by vaginal cytology, sexual maturation in males (preputial separation) and females (vaginal patency), sperm count, motility,

and viability in epididymides, spermatid counts in testes, and primordial follicle counts in ovaries. There is no NOEL for general toxicity. F1 10 mg/kg/day pups had slightly but statistically significantly reduced body weights during the first four weeks of the pre-mating period. Hepatocellular hypertrophy and vacuolation and associated liver weight increases were present in all groups of adult rats, and at 30 to 60 mg/kg/day in F2 weanlings. In males of both generations, absolute liver weights were significantly elevated in dose-related fashion. F1 males had dose-related increased incidence and degree of epididymal mononuclear cell infiltration at all dose levels, with no other associated findings at any dose tested. Common findings at 30 mg/kg/day and above included dose-related adult body weight decrements (especially F1 males), pup body weight decrements, and hepatocellular pigmentation and single cell necrosis. The highest dose level substantially reduced growth and survival of pups. Reproductive findings were either associated with maternal toxicity, were accompanied by general growth delays in young rats, or were of no evident functional importance, so that no adverse effects are indicated. The study is acceptable. Aldous, 2/26/98.

**50221-033 054870** Schwetz, B. A., et al., "Results of a reproduction study in rats maintained on diets containing pentachlorophenol sample XD-8108.00L" (Dow Chemical, USA, 11/7/74). Pentachlorophenol, 90.4%. 10 males and 20 females at 0, 3, 30 mg/kg/day in diet for 62 days before mating, 15 days mating, gestation and lactation, only 1 generation. Apparent parental toxicity NOEL = apparent reproductive effects NOEL = 3 mg/kg/day. Possible adverse effects at 30 mg/kg/day: reduced gestation and lactation survival; reduced newborn and weanling body weight; general increase in abnormalities of pups at weaning, particularly skeletal effects. Apparent parental toxicity was limited to minor decrement in maternal weight gain during weaning period. **Unacceptable, not upgradeable:** due principally to the very limited study design (only one generation, too few doses, too few adult males, treatment period too short, no histopathology of treated adults). C. Aldous, 7/6/87, 6/12/89 (see June 1989 CDFA Rebuttal Response), 6/13/95 (editing changes of 1-liner only).

50221-038 073639 Schwetz, B.A., et al., "Results of two-year toxicity and reproduction studies on pentachlorophenol in rats", B. A. Schwetz et al. Chapter in a volume entitled Pentachlorophenol: Chemistry, Pharmacology, and Environmental Toxicology, K. R. Rao, Ed., New York, 1978. [Dow Chemical U.S.A., Midland, MI]. Published summary of 032:054848 [chronic] and 033:054870 [reproduction]. No worksheet needed. C. Aldous, 6/13/89.

50221-051 136848 Knudsen, I. et al., "Short-term toxicity of pentachlorophenol in rats", Toxicology 2:141-152 (1974). PCP, purity not stated, was administered to weanling Wistar SPF rats (10/sex/group) in diets at 0, 25, 50, or 200 ppm for 12 weeks. Liver and thyroid weights were elevated in high dose females. High dose males had increased liver centrilobular vacuolation. Several reproductive organs were examined microscopically, including ovaries, uterus, testes, and prostate gland. All were reported to have normal appearance. **Unacceptable, not upgradeable** (test article not characterized, and presumed not equivalent to domestic, modern technical; study was not designed to meet "guideline" requirements, no QA or GLP statement, etc.). **No adverse effects indicated.** Report was submitted with reference to reproduction data gap. Aldous, 6/12/95 (no worksheet).

50221-055 148860 Inquiry about basis for appropriate dose level setting for upcoming reproduction study (subsequently resolved by telephone). Aldous, 3/13/97.

**NOTE: THE FOLLOWING STUDY WAS SUBMITTED SUPPLEMENTARY  
TO REPRODUCTION STUDY DATA WAIVER REQUEST:**

50221-038 073636 Kociba *et al.*, "Toxicological evaluation of rats maintained on diets containing pentachlorophenol sample XD-8108.00L for 90 days". Dow Chemical Co., Midland, MI, 3/3/73. Ten Sprague-Dawley rats/sex treated in diet with 0, 1, 3, 10, or 30 mg/kg/day of a PCP grade comparable to Dowicide EC-7 [88 to 93% purity]. Study included microscopic examinations of "gonads" and "accessory sex glands". No microscopic changes appeared to indicate treatment effects. No adverse effects indicated. NOEL = 3 mg/kg/day (increased relative liver weights in both sexes at 10 and 30 mg/kg/day). Also, relative kidney weights were slightly increased at 30 mg/kg/day in both sexes. Study **not acceptable, and not upgradeable** (no QC or GLP assurance, no individual data for most parameters, no summary tabulated data for tissues evaluated histopathologically, limited clinical chemistry parameters, other guideline deficiencies), but useful information. C. Aldous, 6/9/89; re-examined by Aldous with editing of 1-liner, 6/13/95.

50221-051 136850 Christian, M.S., "A critical review of multigeneration studies", Journal of the American College of Toxicology **5** 161-180 (1986). The review examined an extensive database of published rat reproduction studies. Possibly relevant citations were screened to find those which met certain minimal criteria for comparison. For example, further consideration was given only to multiple-generation (i.e., 2 or more) studies with at least 4 animals per treatment group and at least 10 and 60 days pre-mating dose exposure for females and males, respectively. The rat was the only species with sufficient numbers of studies for further analyses. Particular attention was given to the 20 usable studies in which effects observed in the second generation were either not existent or were less severe in the first generation. All 20 of these studies found primary litter reproductive effects in the first generation. In the studies sampled, primary litter reproductive effects were regularly more sensitive endpoints than adult primary reproductive effects. Some studies with primary reproductive effects which were more severe in the second generation utilized test articles which bioaccumulate [one example was hexachlorobenzene, a contaminant in PCP]. Dr. Christian concluded that the chief value of multigeneration studies is to identify primary reproductive effects in adults and offspring. One generation, single litter studies were considered by the author to be adequate to detect reproductive effects, in the absence of bioaccumulation. Aldous, 6/13/95 (no worksheet).

### TERATOGENICITY, RAT

**\*\*50221-047 131037** Hoberman, A.M., "Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of pentachlorophenol administered orally via gavage to CrI:CD:\*BR VAF/Plus\* presumed pregnant rats", Argus Research Laboratories, Inc. (Protocol No. 2119-003), 1/20/94. CrI:CD:\*BR VAF/Plus\* rats, 25/group, were dosed by gavage with PCP (88.9%) in corn oil at 0, 10, 30, and 80 mg/kg/day from days 6-15 p.c. Maternal NOEL = 30 mg/kg/day (body weight and food consumption decrements). Developmental NOEL = 30 mg/kg/day [increased fetal resorptions, decreased fetal weights, a modest incidence of malformations (gastroschisis, hydrocephaly, and diaphragmatic hernia) judged to be treatment-related, although not statistically significant; significant increase in incidence of dilated pelves, and of delayed ossification in several areas, and **increased** mean numbers of thoracic vertebrae and associated increased incidence of 14th ribs]. **Acceptable. "Possible adverse effect"** (due to

the fetal resorptions, decreased fetal weights, ossification delays, and malformations: which findings cannot be assured to result strictly from maternal toxicity). Aldous, 7/28/94.

NOTE: Previously, studies 033:054867 and 036:063202 were taken together to satisfy the rat teratogenicity study data requirement (see Summary of Toxicology Data of Oct., 1988). The recent Argus study (above) is also considered to indicate a "possible adverse effect", however the study NOEL is high compared to the earlier studies (below). The recent study should have primacy in risk assessment, because it represented current technical PCP, employed gavage route, and otherwise meets current standards. Aldous, 7/28/94.

**50221-033 054867** Schwetz, B.A. *et al.*, "The effect of purified and commercial grade pentachlorophenol on rat embryonal and fetal development" [Toxicol. Appl. Pharmacol. **28**:151-161 (1974)]. Dow Chemical Co. (Midland). Sprague-Dawley rats gavaged with corn oil, purified PCP (98+% A.I. at 5, 15, 30, or 50 mg/kg/day) or commercial PCP (88.4% A.I. at 5.8, 15, 34.7, or 50 mg/kg/day). Dosing was p.c. days 6-15 for all of the above dose levels. Additional dams were treated in early or late organogenesis periods (days 8-11 or days 15-15) at a single effective dose level (30 or 34.7 mg/kg/day for purified or commercial PCP, respectively). Maternal toxicity NOEL = 15 mg/kg/day ("purified grade") and 34.7 mg/kg/day (commercial grade), based on body weight gain decrements. No NOEL for developmental toxicity (delayed ossification of skull with "purified grade"). In addition, marked resorptions at 30 or 34.7 mg/kg/day and above for both grades. A preponderance of survivors were males at the highest doses. Several fetal changes including developmental delays, and rib and vertebral anomalies at 15 mg/kg/day and above. **Unacceptable:** principally due to lack of a NOEL in purified grade, which is presumably the most relevant test article in light of current EPA purity standards for PCP. The above developmental changes in the absence of marked maternal toxicity constitutes a "**possible adverse effect**" C. Aldous, 7/3/87. (One-liner revised without new worksheet on 6/13/95 by Aldous).

50221-051 136846 Noted as exact duplicate of 054867, above.

**50221-036 063202** Welsh *et al.*, "Teratogenic potential of purified pentachlorophenol and pentachloroanisole in subchronically exposed Sprague-Dawley rats". Fd. Chem. Toxicol. **25**:163-172 (1987). By FDA Division of Toxicology and Mathematics, Washington, D.C. Test article was Aldrich PCP, 99+% purity, further purified by solvent extraction and recrystallization. Maternal NOEL = 200 ppm (13 mg/kg/day), based on reduced weight gain, clinical signs such as ringed eye and possibly vaginal hemorrhaging. Developmental effects NOEL = 60 ppm (4 mg/kg/day), based on reduced fetal weights, misshapen centra, and a possibly treatment-related increase in resorptions (significant increase in females with >2 resorptions). At 600 ppm (43 mg/kg/day) all but one dam suffered total litter losses due to early resorptions. **Possible adverse effect:** (Developmental toxicity NOEL relatively low and observed in absence of maternal toxicity). This study is not independently acceptable, but contributes to acceptability of rat teratology study 033:0054867 by supplying a NOEL for developmental toxicity for purified PCP in a scientifically valid (although not independently guideline-acceptable) study. C. Aldous, 9/28/88; minor editing changes by Aldous, 6/12/95.

50221-051 136849 Noted as exact duplicate of Record No. 063202, above.

50221-033 054869 "The effect of tetrachlorophenol and pentachlorophenol on rat embryonal and fetal development" (B. A. Schwetz and P. J. Gehring, Toxicol. Appl. Pharmacol. **25**:455

(1973). 1-paragraph abstract, the portion on PCP apparently relates to 50221-033:054867, above. No more information required of this abstract. C. Aldous, 7/6/87, handwritten worksheet only.

### TERATOGENICITY, GOLDEN SYRIAN HAMSTER

**50221-033 054868** "Fetotoxic effects of pentachlorophenol in the Golden Syrian Hamster" (D. K. Hinkle, sponsored by F. K. Kinoshita) Toxicol. Appl. Pharmacol. 25:455 (1973). 1-paragraph abstract. Oral doses of 1.25 to 20 mg/kg/day. Fetal deaths and/or resorptions observed in "3 of the 6 groups" tested. C. Aldous, 7/6/87, handwritten worksheet only. Insufficient information for meaningful DPR evaluation. (Study was addressed in connection with Oct. 1988 Rebuttal Response, but no new worksheet was created; C. Aldous, 10/4/88).

### TERATOGENICITY, RABBIT

\*\*50221-046 131033, Hoberman, A.M., "Developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of pentachlorophenol administered orally via stomach tube to New Zealand White rabbits", Argus Research Laboratories, Inc. (Protocol No. 2119-002), 1/20/94. Technical PCP, Lot Nos. EL-064 (88.9% purity) and JJ-022 (88.1% purity) was administered at 0, 7.5, 15, and 30 mg/kg/day, with 20 does/group. Maternal NOEL = 7.5 mg/kg/day (transient, slight decrement in body weight gain). Developmental NOEL = 30 mg/kg/day (no treatment effects). The 7/24/94 review classified the study as not acceptable, based on concerns that the dosage range was not adequate. Data from the pilot study (i.e. Argus study: Protocol 2119-002P) was requested. That report (Record No. 133543, below) also found modest body weight gain decrements and diet consumption decrements in the range of 20 to 30 mg/kg/day, allowing an upgrade of the primary study to **acceptable. No adverse effects are indicated.** Aldous, 7/27/94 and 1/20/95.

50221-050 133543 Hoberman, A.M., "Dose-range developmental toxicity (embryo-fetal toxicity and teratogenic potential) study of pentachlorophenol administered orally via stomach tube to New Zealand White rabbits". Pilot to Document No. 50221-046, Record No. 131033. Argus Research Laboratories, Inc., Protocol No. 2119-002P. Date of pilot study: 3/30/93. Five pregnant rabbits/dose were dosed with 0, 5, 10, 20, and 30 mg/kg/day from gestation days 6 through 18. The best evidence of a treatment effect in the range of 20 to 30 mg/kg/day was a decrement in diet consumption and associated maternal body weight decrement compared to controls and 5 to 10 mg/kg/day groups. Although the pilot study does not provide independent evidence of treatment effects at 20 to 30 mg/kg/day, the data are sufficiently consistent with the primary study data to justify the use of 30 mg/kg/day as the high dose level for the primary study. Aldous, 1/20/95.

### GENE MUTATION

\*\*50221-030 067571 "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Pentachlorophenol in B6C3F1 mice." (Mutagenicity studies incorporated into report of mouse oncogenicity study: this mutagenicity study performed at EG&G Mason Research Institute, 1983? in Draft report dated 4/88.) Technical pentachlorophenol, 91.6%; tested with Salmonella typhimurium strains TA1535, TA1537, TA98 and TA100, with rat and hamster liver activation and without activation, two trials, triplicate plates each trial, 20 minute preincubation before

plating; tested at 0 (DMSO), 0.3, 1, 3, 10 or 30 mg/plate; no increase in reversion rate; acceptable. Gee, 9/28/88.

**\*\*50221-036 063203** "In vitro Microbiological Genotoxicity Assays of Pentachlorophenol and 2,4,5-T Acid." (SRI, 4/79) PCP (pentachlorophenol) no purity stated, tested in five strains of Salmonella typhimurium - TA1535, TA1537, TA1538, TA98 and TA100 with and without rat liver activation, duplicate plates, two trials; tested at 0 (DMSO), 1, 5, 10, 25, 50 or 100 mg/plate; cytotoxicity at higher concentrations. Originally unacceptable (no purity stated). Upgraded on receipt of test article characterization in 038:073634 [see supplementary worksheet upgrading study 036:063203 (DNA Damage aspect of same SRI report), dated 6/12/89]. E. coli WP2 was also negative for tryptophan revertants. Gee, 9/23/88, C. Aldous, 6/12/89.

50221-033 55359 "Evaluation of herbicides for possible mutagenic properties" (K. J. Anderson et al., J. Agr. Food Chem. 20:649-656, 1972). PCP reported negative in point mutation studies in S. typhimurium and E. coli. **Not acceptable nor upgradeable**: Study conditions not defined, test article not likely to reflect current purity standards for technical PCP. C. Aldous, 7/6/87, worksheet handwritten, not on disk.

### CHROMOSOME EFFECTS:

**\*\*50221-030 067571** "NTP Technical Report on the Toxicology and Carcinogenesis Studies of Pentachlorophenol in B6C3F1 mice" [Board draft] (Mutagenicity studies incorporated into report of mouse oncogenicity study: chromosome effects studies performed at Columbia University, data presented in Galloway et al., Environ. Molec. Mutagen. 10 (Suppl. 10): 1-175 (1987).) Technical pentachlorophenol, 91.6%; tested with Chinese hamster ovary cells for sister chromatid exchanges and for chromosomal aberrations. Sister chromatid exchange: Tested at 0 (DMSO), 1, 3, 10 or 30 mg/ml without activation for 26 hours, at 0, 3, 10, 30 or 100 mg/ml with rat liver activation for 2 hours followed by further 26 hours incubation; scored 50 mitotic cells per concentration in the second mitosis; "weakly positive" results without activation, negative with activation. Chromosomal aberrations: Tested at 0 (DMSO), 10, 30 or 100 mg/ml without activation for 8 hours, at 0, 3, 10, 30 or 100 mg/ml for 2 hours with activation followed by a further 10 hours incubation in trial 1, at 0, 10, 60, 70 or 80 mg/ml with activation in trial 2; negative results without activation, "weakly positive" results with activation in trial 1 and "equivocal" results in trial 2; possible adverse effects. Acceptable. Gee, 9/28/88.

### DNA DAMAGE

**\*\*50221-036 063203** "In vitro Microbiological Genotoxicity Assays of Pentachlorophenol and 2,4,5-T Acid." (SRI, 4/79) Pentachlorophenol (Dowicide EC-7, 88%); tested with Saccharomyces cerevisiae with and without rat liver activation, two trials, 5 plates for mitotic recombination per concentration; 4 hour incubation at 0 (DMSO), 0.001, 0.005, 0.01, 0.02 or 0.05 w/v; increased frequency in mitotic recombinants with concentration; disc (6 mm) assay without activation only with E. coli strains W3110 (polA<sup>+</sup>) and p3478 (polA<sup>-</sup>) and B. subtilis strains H17 (rec<sup>+</sup>) and M45 (rec<sup>-</sup>), duplicate plates, four trials, amounts of 0.01, 0.05, 0.5, 1.0 or 5.0 mg applied per disk and incubated 16 - 17 hours and the zone of inhibition of growth measured; with B. subtilis, a greater zone of inhibition was reported for the rec<sup>-</sup> strain compared with the rec<sup>+</sup> strain in several trials at several concentrations; with E. coli, the pol<sup>-</sup> strain had a smaller zone of

inhibition suggesting repair with the polA<sup>+</sup> enzyme caused more extensive damage. Initially unacceptable due to inadequate characterization of the test material. **Acceptable**, on receipt of test article characterization (038:073634). Gee, 9/27/88; Aldous, 6/12/89.

50221-266 159038 Micronucleus tests (rat and mouse), very briefly reported in appendix of the report: "NTP technical report on the toxicology and carcinogenesis studies of pentachlorophenol (CAS No. 87-86-5) in F344/N rats (feed studies)". Micronucleus studies were done at Integrated Laboratory Systems, evidently in 1993. Male F344/N rats and male B6C3F<sub>1</sub> mice were dosed once daily ip for 3 days with PCP (purity not specified) at 0, 25, 50, or 75 mg/kg/day (rats) or 0, 50, 100, or 150 mg/kg/day (mice). Animals were sacrificed 24 hr after the last injection. Positive controls were dosed ip with cyclophosphamide at 25 (rats) or 50 (mice) mg/kg/day. There were 5 animals assigned per treatment. All rats and mice in respective high dose groups died. Analyses of micronuclei from bone marrow PCE's of survivors did not indicate treatment effects. Study is not acceptable (too few animals, one sex only without justification, and other deficiencies) and not upgradeable. No adverse effects indicated. Aldous, 1/16/98.

### MUTAGENICITY, GENERAL

Note that the following studies were summarized in 50221-266 159038: *S. typhimurium* plate assay (50221-030 067571), and chromosomal aberration study (50221-030 067571).

### NEUROTOXICITY (Not required at this time.)

### MISCELLANEOUS STUDIES (NOT SB-950 MANDATED)

50221-049 132455 Hematology, clinical chemistry, and limited neurotoxicity study data on mice (study durations up to 6 mos) were provided by the U.S. Public Health Service to Dr. Goodman of DPR for purposes of risk assessment. These data represented 30-day and 6-month subacute and subchronic segments of the NTP mouse dietary study, for which the 2-year main portion was reviewed under DPR Record Nos. 067571 and 075632. The 4-week study utilized 3 grades of PCP: (1) purified, (2) technical, and (3) Dowicide EC-7, at dose levels from 20 to 12,500 ppm. The latter dose level led to 100% mortality except for technical grade (which proved fatal to 14/19 males and 7/15 females within the 30-day period). The 6-month study involved the same test articles, plus an additional Dow product: DP-2. The 6-month study used a narrower dosage range (maximum dose levels of 1200 to 1800 ppm, depending on the relative toxicities of the respective grades). RESULTS: The 4-week hematology data were generally negative, except that technical PCP elevated platelet counts in both sexes consistently at week 4 in the dose range of 20 to 500 ppm. There was no comparable platelet effect at 6 months. The 4-week clinical chemistry data were consistent with liver toxicity (elevated parameters: SGPT, alkaline phosphatase, cholesterol, and albumin). Similar changes were noted at 6 months. In both time periods, respective LEL's for clinical chemistry changes were about 500 to 600 ppm. Following 6 months of treatment at 1200 ppm with Dowicide EC-7 there was an apparent increase in mean startle response in females only. This was not observed in either sex following treatment with technical PCP for 6 months. Statistically significant elevations in motor activity were observed in 200 ppm males and in 600 ppm females administered technical PCP for 6 months, and non-significant increases were seen in 600 ppm males and in 200 ppm females. Collectively, these

functional or behavioral changes should be considered treatment-related. Aldous, 1/23/95 (no worksheet).

**50221-032, 033** 054849-51, 055406 "The chronic toxicity of technical and analytical pentachlorophenol in cattle. I. Clinicopathology". NIEHS; Environmental Biology Branch, Chemistry Branch, and Biometry Branch; Research Triangle Park, NC, and vicinity. Toxicol. Appl. Pharmacol. 52:468-490, (1980). Three Holstein heifers (approx. 1 year old) per group were exposed for 160 days to a) control diet, or 15 mg/kg/day\* of b) 100% analytical grade PCP, or c) 90% analytical/10% technical PCP, or d) 65% analytical/35% technical PCP, or e) 100% technical PCP. No NOEL obtained. Technical was typically more toxic than was analytical. Weight gain decrements were roughly dose-related in technical PCP groups. "Unthrifty" appearance and reduced disease resistance in 100% technical group. Generally dose-related decrease in blood values (RBC count, HCT, Hb) in 35% and 100% technical groups. Gamma-glutamyl transpeptidase was reduced in dose-related manner in all technical groups. Liver hypertrophy, increases in SER, increases in specific MFO activities, bile duct/gall bladder hypertrophy were seen in 100% technical group, and frequently in all groups receiving technical PCP. Thymus was markedly reduced in size in all PCP groups. "Villous-like" hyperplasia in 100% technical group urinary bladders, with associated thickening of mucosal epithelial lining of ureters, renal pelves and papillae, and terminal portions of collecting ducts.  
\*Total PCP for groups b-e was 20 mg/kg/day from days 1-42, then reduced to 15 mg/kg/day for balance of study. C. Aldous, 7/2/87.