

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

PENTACHLORONITROBENZENE (PCNB)

SB 950-088, Tolerance # 291

Chemical Code: 464

October 29, 1987

Revised: 10/16/89, 9/27/90, 1/14/93, 7/10/95

I. DATA GAP STATUS

Chronic rat:	No data gap, possible adverse effect
Chronic dog:	No data gap, no adverse effect
Oncogenicity rat:	No data gap, possible adverse effect
Oncogenicity mouse:	No data gap, possible adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratogenicity, rat:	No data gap, no adverse effect
Teratogenicity, rabbit:	No data gap, no adverse effect

Gene mutation: No data gap, no adverse effect.
Chromosome effects: No data gap, possible adverse effect.
DNA damage: No data gap, no adverse effect.
Neurotoxicity: Not required at this time.

Note: Toxicology one-liners are attached.

** indicates acceptable study

Boldface indicates possible adverse effect

Revised by G. Chernoff, 9/27/90; Kellner, 1/14/93, Aldous, 7/10/95.

File name: T950710

All relevant records on file with the DPR library as of March 2, 1995 are included in this summary. This includes records through Record No. 130986, Document No. 291-131. (C. Aldous, 7/10/95)

These pages contain summaries only. Each individual worksheet may contain additional effects.

II. TOXICOLOGY SUMMARY

Many tests utilized PCNB which was contaminated with hexachlorobenzene (HCB) at levels above those currently allowed (see January 1987 EPA document on guidance for registration). The new studies employ purer (low HCB) material than the earlier studies. A final evaluation of the PCNB effect should be based on the results of tests using the material currently in production (Harnois, 10/87).

A recent study (DPR Record No. 127174, the 1993 Exxon study, below) did not provide definitive evidence of oncogenicity at dose levels up to 500 to 1000 mg/kg/day, 5 days/week; whereas another recent study (Record No. 098120, the 1991 IRDC study, below) found clear follicular tumor effects in the dose range of 3000 to 6000 ppm in males and at 6000 ppm in females. In the Exxon study, 500 mg/kg/day (5 days per week) led to more than the expected number of thyroid tumors in males, but twice that dose level led to only 1 thyroid tumor (less than the historical control average). Despite the lack of consistent indications of oncogenicity in the Exxon study, parenchymal cells of both liver and thyroid underwent dose-related hypertrophy, a condition often associated with neoplasia in either of these tissues. The IRDC study utilized PCNB with "less than 0.1% HCB" (p. 280 of Record No. 098120). The Exxon study had a similarly low level of HCB (p. 1824 of Record No. 127174). The Exxon study dosed rats by gavage, while the IRDC study was dietary. Although these two studies utilized PCNB with comparable HCB contamination, other study parameters (dose ranges, method of administration) were sufficiently different that the Exxon study should not override the IRDC study for purposes of hazard assessment. The "possible adverse effect" designation remains for oncogenicity, based on thyroid tumors in rats. Aldous, 6/6/95.

COMBINED RAT

**291-127 127174, Plutnick, R.T., "2-Year chronic toxicity/oncogenicity study in rats with Pentachloronitrobenzene (PCNB) (MRD-89-505)", Exxon Biomedical Sciences, Inc., Nov. 8, 1993. Project ID 250570B. PCNB tech., 98%, was administered orally by gavage at concentrations of

0, 5, 50, 500 or 1000 mg/kg/day to 60 Sprague-Dawley rats/sex/group for up to 2 years (5 days/week). A conservative NOEL = 5 mg/kg, based solely on hepatocellular hypertrophy in 50 mg/kg males. Common findings at 500 to 1000 mg/kg included hepatocellular hypertrophy and thyroid hypertrophy of the follicular epithelium, and marked decreases in activity of circulating alanine aminotransferase (each of these changes in both sexes). The report contained a "flagging statement" relating to increased thyroid follicular tumors in 500 mg/kg males (but not 1000 mg/kg males), and increased "fatal" hepatocellular tumors in 1000 mg/kg males. Neither the investigators nor the DPR reviewer considers either of these observations to demonstrate treatment effects. Considering the dose levels required to elicit definitive toxicity, no "adverse effects" are indicated. **Acceptable.** Kishiyama and Aldous, 6/5/95.

291-109 116930 Keefe, R.T., "90-Day subchronic study in rats with Pentachloronitrobenzene (MRD-89-505)", Exxon Biomedical Sciences, Inc., Project No. 250570A, 6/9/92. This is a gavage study with dose range comparable to Record No. 127174, above, for which this is evidently the range finding study. Effects in this subchronic study were consistent with the above study. A review of this 90-day study by the DPR Product Data Review Group (by R. Duncan and G. Patterson) is included in the data volume.

****084 098120** "Two Year Dietary Toxicity and Oncogenicity Study in Rats", (E.I. Goldenthal, International Research and Development Corporation, Lab. Project I.D. IRDC 399-072, 8/1/91). Pentachloronitrobenzene (PCNB), purity 99.4%, was administered in the feed at concentrations of 0, 20, 3,000 or 6,000 ppm to 60 Charles River CD* rats/sex/group for 2 years. By study termination, high-dose male and female body weights were 10.5% and 11.5% less than controls, respectively. Food consumption was significantly decreased during the first 20 weeks for high-dose males (6% to 14%) and during the first 8 weeks for high-dose females (up to 7%). Accentuated lobulation of the liver and tan/yellow foci in the lungs occurred with greater frequency in this group. Increased absolute and relative liver and thyroid weight at the mid- and high-dose levels correlated with hepatocellular hypertrophy and thyroid cell hypertrophy and hyperplasia. Chronic NOEL = 20 ppm. **Possible Adverse Effect:** Thyroid tumors (follicular adenoma and carcinoma). ACCEPTABLE. (Kishiyama, Kellner and Gee, 1/13/93).

291-116 120716 Goldenthal, E.I., "90-day dietary toxicity study in rats", IRDC, Report # 399-122, 5 January 1993. Pentachloronitrobenzene (PCNB), 99.1% purity, was administered to male CD* rats in diet for up to 90 days at 0, 20, or 6,000 ppm. Fifteen rats/group were sacrificed after treatment duration of 7, 14, 30, or 90 days; or 90 days treatment plus 90-day recovery period. Parameters examined included body weights; food consumption; clinical signs; serum T3, T4, and TSH; general gross examination; and microscopic examinations of liver, pituitary, and thyroid/parathyroid glands. No NOEL was found: hepatocellular hypertrophy was dose-related at 20 and 6000 ppm after 90 days of treatment. At 6000 ppm, thyroid follicular epithelial hypertrophy was observed at progressively advancing degree of intensity over time. This was accompanied by decreased serum levels of thyroid hormones (T3 and T4), and increased serum TSH. An evaluation by a consultant, C.C. Capen, concluded that thyroid system changes arose as a result of liver microsomal enzyme induction, leading to depletion of thyroid hormones, causing compensatory overstimulation of thyroid follicular cells. Correspondence at the front of this volume indicates that mechanistic studies are underway to substantiate this hypothesis. This is an acceptable ancillary study. No "adverse effects" are indicated by this study. H. Green and C. Aldous, 3/3/95.

291-084 098119 A protocol for Record No. 120716, above.

CHRONIC RAT

014 915659, "Acute and Chronic Toxicity Studies on Pentachloronitrobenzene, III. Effect of adding PCNB to the diet of rats for two years", (published in Arch. Int. Pharmacodyn., 1958, CXIV, no. 1, Finnegan, J.K. et al), 20% dust PCNB; fed in the diet for 2 years at 0, 25, 100, 300, 1000, or 2500 ppm, 10/sex/level. Depressed growth in males at 2500 ppm and females \geq 100 ppm; severity not dose-related. Insufficient information (summary only, too few animals). UNACCEPTABLE, not upgradeable (too few animals, summary information only). (Gee, 5/10/85)
029 017021, Duplicate information to 014 915659.

CHRONIC DOG

NOTE: The overall evaluation of dog chronic toxicity has concluded that no "adverse effects" are indicated, despite indications of "possible adverse effects" in older studies. Considerations were (1) the only accepted study indicated no adverse effects, while characterizing toxicity to the primary target organ (liver), and (2) older studies used PCNB which was potentially much higher in contaminants such as HCB than current technical, and therefore may not be relevant to modern product safety evaluation. Aldous, 6/8/95.

**074 091813 "One year Chronic Dietary Study in Dogs", (E. I. Goldenthal, International Research and Development Corporation, Laboratory Project ID 399-087, 11/16/90). PCNB technical, purity 96%, was fed to 6 beagle dogs/sex/group for 1 year at concentrations of 0 (acetone), 15, 150, or 1500 ppm. Increased relative liver weight (liver/body and liver/brain) and alkaline phosphatase levels were reported as well as decreased alanine aminotransferase. NOEL = 150 ppm (liver hypertrophy at 1500 ppm). No Adverse Effects. ACCEPTABLE. (Kishiyama, Kellner and Gee, 1/13/93).

014 915659, "Acute and Chronic Toxicity Studies on Pentachloronitrobenzene, IV. Effect of Adding PCNB to the Diet of Dogs for One Year", (published in Arch. Int. Pharmacodyn., 1958, CXIV, no. 1, Finnegan, J.K. et al). 20% PCNB, fed in the diet for 1 year at 25, 200, or 1000 ppm, 3 dogs/level. Initial review (Remsen, 5/10/85) noted a possible adverse effect (hepatic cell enlargement in all animals at all levels) and that the study was unacceptable. Subsequent review for tox. summary found insufficient information for evaluation and that the study was UNACCEPTABLE, not upgradeable (no negative control, too few and uncharacterized animals, summary information). (Harnois, 9/16/87)

028 029679, summary of 014 915659.

029 017022, duplicate information to 014 915659.

014 915700, "Toxicologic Study on the Effect of Adding Terraclor to the Diet of Beagle Dogs for a Period of Two Years", (Department of Pharmacology, Medical College of Virginia, 6/10/68). PCNB (98.2%; 1.4% HCB) in diet at 0, 5, 30, 180, or 1080 ppm, for 2 years; 4

dogs/sex/level. 1/sex/dose necropsied at 12 months; rest survived to 24 month necropsy. Initial review (Remsen, 5/10/85) noted **adverse effects** (increased liver weight at 1080 ppm; cholestatic hepatitis with secondary bile nephrosis at 180 and 1080 ppm;) unacceptable (missing histopathology data, no diet mix analysis, no dose justification). Review of histopathology data (043381; G. Patterson, 10/9/86) found data UNACCEPTABLE; review of all data on file (Harnois, Martz 9/87) found microscopic cholestatic changes at 30 ppm; presumptive NOEL = 5 ppm; study UNACCEPTABLE, not upgradeable (no analysis of diet mix, no ophthalmological exam, inadequate clinical chemistry tests).

033 043381, Histopathology data submitted for 915700.

036 050839, Feed consumption; urine and blood sample analyses for 915700.

014 020395, summary of 014 915700.

028 029682, summary of 014 915700.

EPA one-liner: NOEL = 30 ppm, LEL = 180 ppm. Cholestatic hepatitis, secondary bile nephrosis. Minimum.

015 915698, "Chronic Oral Toxicity of Pentachloronitrobenzene, Two-Year Study with Dogs", (Farbwerke Hoechst AG, # 3587, 10/23/68). PCNB, 98.8% purity, fed in the diet for 2 years at 0, 500, 1000, or 5000 ppm, 3/sex/level. 5/6 dogs in the high dose were killed in moribund condition from 7 to 15 months. **Adverse effects reported** (body weight loss, extensive liver damage, anemia and leucocytosis, and conjunctivitis and ulceration of the cornea reported at 5000 ppm; liver changes at 500 and 1000 ppm and conjunctivitis at 1000 ppm). NOEL < 500 ppm. UNACCEPTABLE, not upgradeable (too few animals, dogs too old at start, excessive mortality at high dose, pathology reported in German). (Gee, 5/14/85)

ONCOGENICITY RAT (note: data gap is filled by a "combined" study, above)

015 915705, "Bioassay of Pentachloronitrobenzene for Possible Carcinogenicity", (National Cancer Institute, NIH, Bethesda, MD., # 3575, 1978). PCNB of about 97% purity, administered in the diet for 78 weeks, 50/sex/group, at a low dose range for males between 5000 and 7500 ppm (5417 ppm TWAC), for females between 7250 and 11000 ppm (7875 ppm, TWAC), and a high dose range between 10000 and 15000 ppm (10064 ppm, TWAC) for males and between 14500 and 22,000 ppm

(14635 ppm, TWAC) for females, with 20/sex/group at 0 ppm. Decreased body weight at both dose ranges in females and males. No adverse effects reported but there was insufficient information for analysis; UNACCEPTABLE, not upgradeable (too few control animals, dosing schedule does not follow guidelines, incomplete histopathology). (Gee, 5/15/85)

028 029685, Summary of 015 915705.

026 915707, Partial duplicate of 015 915705.

EPA one-liner: Oncogenic NOEL > 10,064 ppm (male) (HLT); > 14,635 ppm (female) (HLT). Doses fluctuated throughout the course of the study so the NOEL's are time weighted averages. Minimum.

015 915703, "Carcinogenicity Study with Pentachloronitrobenzene (PCNB) in Rats", (Central Institute for Nutrition and Food Research, # 4442, August 1974). PCNB technical, 98.3% purity (2.7% HCB), fed in the diet for 104 weeks at 0, 100, 400, or 1200 ppm, 50/sex/group. **Adverse effects** reported (increased liver weight at 1200 ppm and non-neoplastic liver changes at all dose levels). Apparent NOEL < 100 ppm. UNACCEPTABLE, not upgradeable (no dose rationale, no feed analysis, incomplete histopathology, no individual data). (Remsen, 5/13/85)

028 029683, summary of 015 915703.

EPA one-liner: Study does not demonstrate non-carcinogenicity since limited histological analysis was performed and since respiratory infection complicated diagnosis of lung neoplasms. NOEL for liver toxicity not established. Supplementary.

ONCOGENICITY MOUSE

014 915702, "Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note", (Bionetics Research Laboratories, Inc., Litton Industries, Bethesda, MD., 1969; published in Journal of the National Cancer Institute, vol. 42, no. 6, June 1969, Innes,

J.R.M. et al). PCNB, no purity stated, given by gavage in 0.5% gelatin to 36/sex from age 7 days to 4 weeks; then fed in the diet until age 18 months at 0 and 464 mg/kg (MTD). Positive controls included Urethan, Amitrol, Aramite, Dihydrosafrole, Isosafrole, and Safrole. **Adverse effects** reported (liver tumors). UNACCEPTABLE, not upgradeable (too few animals, only one dose level, no supporting data for dose justification, no differentiation between malignant and benign tumors). (Remsen, 5/10/85)

EPA one-liner: High contamination with the known carcinogen HCB (11%).
Determination of carcinogenic potential. Supplementary.

015 038729, "Bioassay of Pentachloronitrobenzene for Possible Carcinogenicity", (National Cancer Institute, NIH, Bethesda, MD., # 3575, 1978). PCNB ~ 97% purity, administered in the diet for 78 weeks at a low dose range between 1075 and 3000 ppm (2606 ppm TWAC) and a high dose range between 2150 and 6000 ppm (5213 ppm, TWAC) with 50 males/group, and with 50 females/group at a low dose range between 2320 and 4500 ppm (4093 ppm, TWAC) and a high dose range between 4640 and 9000 ppm (8187 ppm, TWAC), with 20/sex/group at 0 ppm. **Adverse effects** reported (hepatocellular carcinoma in females at 3000 ppm). UNACCEPTABLE, not upgradeable (too few control animals, dosing schedule does not follow guidelines, incomplete histopathology). (Remsen, 5/15/85).

026 046895, Partial duplicate of 015 038729.

028 046896, Summary of 015 038729.

EPA one-liner: Study does not demonstrate non-carcinogenicity since a limited number of animals survived to the end of the test. Carcinogenicity NOEL = 5213 ppm (male) (highest level tested); 8187 (female) (highest level tested). Supplementary.

015 915704, "Pentachloronitrobenzene (PCNB), Carcinogenicity Study in Mice", (Central Institute for Nutrition and Food Research, # 4365, April 1974). PCNB technical 98.3% purity, administered in the diet for 80 weeks at 0, 100, 400, or 1200 ppm, 100/sex/level. **Adverse effects** reported (decreased body weights in males at 1200 ppm, increased liver weights in both sexes at 400 and 1200 ppm, increased kidney weights in females at 1200 ppm, subcutaneous

fibrosarcomas in females at 1200 ppm, and liver neoplasms in males at 100, 400, and 1200 ppm).

UNACCEPTABLE (no individual data, no dosage analysis) not upgradeable. (Remsen, 5/13/85)

028 029684, summary of 015 915704.

EPA one-liner: Oncogenic NOEL < 1200 ppm (female) (increased incidence of subcutaneous fibrosarcomas, Q = 2.43 (ppm)⁻¹). Minimum.

014 915701, "Tumor Initiatory Activity of Some Chloromononitrobenzenes and Other Compounds", (University of Birmingham, England, published in Cancer Research 26, 12-17, January 1966, Searle, C.E.). PCNB (technical was 2x crystallized); 0.2 ml of 0.3% in acetone or acetone alone applied to the clipped backs of mice (10/sex) 2x week for 12 weeks; all animals were then treated with croton oil for 20 weeks, held for 20 weeks without treatment, and necropsied. **Adverse effects** reported (skin tumors). UNACCEPTABLE, not upgradeable (too few animals, no animals without promoter, no histopathology). (Harnois 9/3/87)

EPA one-liner: 0.2 ml of 0.3% PCNB resulted in multiple papillomas. Purity of PCNB unspecified.

038, 052- 056428, 056997, 069308, "Toxicology and Carcinogenesis Studies of Pentachloronitrobenzene in B6C3F₁ Mice (feed studies)", (EG & G Mason Research Institute, NIH Publication No. 87-2581, January, 1987). PCNB (> 99% AI; < 0.07% hexachlorobenzene) fed in the diet for 103 weeks to 50/sex/group at 0, 2,500, or 5,000 ppm. No adverse effects from test substance reported. NOEL (males) ≥ 5000 ppm; NOEL (females) not determined (Klebsiella infection increased death, lesions; decreased body weight). Initially reviewed as not acceptable (2 dose levels, no organ weights, missing tissues for histopath. exam, no blood smears, questionable maximum dose, effects from infectious agents). (Harnois, 10/5/87). UNACCEPTABLE and not upgradeable with survival time complicated by disease. (Kishiyama, 6/12/89 and Gee, 10/13/89).

052 069038, Supplement to 056997.

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/2/89) notes EPA classification as "Core Minimum".

NOTE: Although there are several studies in this category, none is adequate alone to fill the data gap. Collectively, however, there is an adequate body of data for evaluation, based on the most recent study by NTP with the supplemental data in 069308. Two of the three studies produced in 1974 or later and employing PCNB purity of 97% or greater indicated liver tumors, the most consistent finding of interest. The "possible adverse effect" remains, even though the most recent of these studies (NIH Publication 87-2581) was negative for oncogenicity. (Harnois, 10/87; Gee, 10/89; and Aldous, 7/10/95).

REPRODUCTION, RAT

082 096242 "Two Generation Reproduction Study in Rats", (J.L. Schardein, International Research and Development Corporation, IRDC Project #399-086, 2/1/91). PCNB (99.56%) was incorporated in the feed at concentrations of 0 (control), 20, 3000, or 6000 ppm to 26 Charles River COBS* CD* rats/sex/group for 2 generations. Body weights for 3000 and 6000 ppm F0 females and their respective F1a and F1b pups were significantly lower than control. Similar differences in weight were also seen in F1 adults and F2a, F2b litters. Food consumption was reduced 14% and 25% for high-dose F0 and F1 parental animals, respectively. Parental NOEL = 20 ppm (reduced parental body weights at mid- and high dose). Reproductive NOEL = 20 ppm (reduced pup weights with no effect on reproductive parameters). **No Adverse Effects. Acceptable. Kishiyama, Kellner and Gee, 1/13/93.

**291-131 130986 Phillips, R. D., "Two generation reproduction toxicity study in rats with Pentachloronitrobenzene (PCNB) (MRD-89-505)", Exxon Biomedical Sciences, Inc., Toxicology Laboratory, East Millstone, NJ., Project ID 150535, June 1, 1994. This was a standard 2-generation (1 litter per generation) study. Groups of 35 Cr1:CD*BR rats/sex/group received 0, 10, 100, or 1000 mg/kg/day PCNB by gavage as an aqueous suspension in 1% CMC and 0.1% Tween 80. Parental NOEL = 10 mg/kg/day, based on thyroid follicular hypertrophy and/or hyperplasia in 100 mg/kg/day males. Reproductive and developmental NOEL = 1000 mg/kg/day = HDT. No NOAEL is indicated, since there were no "adverse effects". Common findings at 1000 mg/kg/day were

hepatocellular hypertrophy, as well as the above thyroid effects. Males were more susceptible in both organs. **Acceptable, with no adverse effects.** H. Green and C. Aldous, 7/7/95.

014 915712, "Three Generation Reproduction Study on Rats Receiving Terraclor in Their Diet", (Department of Pharmacology, Medical College of Virginia, # 2491, 5/17/68). PCNB, 98.2% purity, administered in diet at 0, 5, 50, or 500 ppm with 25/sex/level for 3 generations, 2 litters/generation. Insufficient information for evaluation. UNACCEPTABLE, not upgradeable (no justification for maximum dose, no diet analysis, inadequate numbers of animals and sampling for production of histopathology data). (Remsen, 5/10/85).

014 020395, Summary of 014 915712.

028 029681, Summary of 014 915712.

008 046852, Partial duplicate of 014 915712.

EPA one-liner: Reproductive NOEL \geq 500 ppm (highest level tested).

NOTE: The memo from EPA to CDFA addressing differences in data gap status for this chemical (dated 2/2/89) notes EPA classification as changed from "Core Minimum" to "Core Supplementary".

TERATOLOGY, RAT

**057 074794, "Developmental Toxicity Study in Rats", (K.A. Keller, I.R.D.C., Laboratory Project ID 399-068, 4/11/88). PCNB Technical, Lot #MDD 080687, 97.3%, (0.025% HCB), was administered by gavage to groups of 25 mated COBS:CD SD female rats at dose levels of 0 (0.2% high viscosity carboxymethylcellulose vehicle control), 30, 600, or 1200 mg/kg/day on days 6-15 of gestation. There were no clear signs of maternal toxicity at any of the dose levels tested. Using the fetus as the unit of comparison, there was a marginal, but statistically significant, increase in resorptions at 30, 600, and 1200 mg/kg without significant decrease in live fetuses per litter. Mean numbers of resorptions in the treatment groups did not differ significantly from controls, and were within the historical control range. Maternal NOEL = 1200 mg/kg/day (HDT); Developmental NOEL < 30 mg/kg/day (marginal increase in

resorptions); Developmental NOAEL = 1200 mg/kg/day (HDT). The study is **ACCEPTABLE**, and no adverse developmental health effects are noted (J. Kishiyama and G. Chernoff, 8/29/90).

014 915708, "A Study of the Potential Teratogenic Effects of Pentachloronitrobenzene in Rats", (Medical College of Virginia, # 1856, 7/7/72). PCNB technical, 97.8% purity, administered at 0, 8, 20, 50, or 125 mg/kg/day in corn oil by oral gavage to mated female rats (≥ 20 /group) on days 6 through 15 of gestation (Day 0 = +vaginal smear). No maternal effect reported. Insufficient information for assessment. UNACCEPTABLE, not upgradeable (no justification for apparently inadequate maximum dose). (Remsen, 5/10/85).

028 029680, Summary of 014 915708.

015 038730, Summary of 014 915708.

015 915711, Summary of 014 915708.

EPA one-liner: NOEL > 125 mg/kg (HDT). No maternal toxicity report.
Supplementary. When combined with Courtney rat data rated core minimum. Down grade to supplementary.

014 915709, "Teratogenicity Studies on halogenated Benzenes (Pentachloro-, Pentachloronitro- and Hexabromo-) in Rats", (Health Protection Branch, National Health and Welfare, Ottawa, Canada, published in Toxicology, 5 (1975) 117-122, Khera, K.S. and Velleneuve, D.C.). PCNB, no purity stated, in corn oil at 0, 50, 100, or 200 mg/kg/day administered by oral gavage to mated female rats (20/group) on Days 6-15 of gestation (Day 0 = + vaginal smear). Insufficient information for assessment. UNACCEPTABLE (no purity data, no justification for apparently inadequate maximum dose, no individual data); not upgradeable. (Remsen, 5/13/85)

EPA one-liner: The report is a summary of the study and suggests that a NOEL for maternal toxicity is 100 (effect not clearly defined). No fetal effects were reported.
Supplementary.

015 915710, "The Effects of Pentachloronitrobenzene, Hexachlorobenzene, and Related Compounds on Fetal Development" (Pesticides and Toxic Substances Effects Laboratory, EPA, Research Triangle Park, N.C., published in Toxicology and Applied Pharmacology 35, 239-256 (1976),

Courtney, K.D. et al.) PCNB (11% HCB), PCNB (99% AI) in corn oil/acetone at 0 and 500 mg/kg was administered by oral gavage to mated female CD rats on Days 7-18 of gestation (Day 1 = + vaginal plug or smear). Examined 5-7 litters/group. Insufficient information for evaluation. UNACCEPTABLE, not upgradeable (inadequate description of test and results, too few litters examined.) (Harnois, 9/17/87).

TERATOGENICITY, MOUSE

015 915710, "The Effects of Pentachloronitrobenzene, Hexachlorobenzene, and Related Compounds on Fetal Development", (Pesticides and Toxic Substances Effects Laboratory, EPA, Research Triangle Park, N.C., published in Toxicology and Applied Pharmacology 35, 239-256 (1976), Courtney, K.D. et al.) PCNB (11% HCB with tetrachloronitrobenzenes (TCNB), 0 or 500 mg/kg in corn oil was given by oral gavage to C57Bl/6 mice on gestation Days 7-11 (Day 1 = + plug or smear). Developmental effects reported as cleft palate, renal agenesis, increased anophthalmia and microphthalmia. No maternal data reported. CD1 mice were given corn oil/acetone (9:1) alone or with PCNB (11% HCB + TCNB), PCNB (artificial mix, 11% HCB + TCNB), PCA (a metabolite), TCNB, and HCB on Days 7-16. HCB (100 mg/kg) was associated with increased maternal liver size; developmental effects noted as renal agenesis, small kidney, cleft palate. PCNB (500 mg/kg) was associated with clubfoot and cleft palate as well as decreased fetal weight, abortions, maternal deaths and maternal weight loss; no effect from PCA or TCNB. Initial review (Remsen, 5/14/85) noted PCNB effects as adverse and study as UNACCEPTABLE. Review for preparation of tox. summary noted insufficient information for evaluation of PCNB effect (absence of maternal findings for C57Bl/6 strain and PCNB, developmental effect present only at concentrations giving maternal effects for CD1 strain, too few dose levels, too few animals, no justification for dose levels, unclear relationship of tested substance to proposed marketed substance, summary report). UNACCEPTABLE, not upgradeable. (Harnois, 9/17/87)

EPA one-liner: In C57Bl/6 mice on PCNB with high HCB contamination, there was an unstated incidence of renal agenesis. Insufficient detail provided; inadequate data. In CD-1 mice there were no kidney effects. There were 26% cleft palates in 8 of 10

litters on 500 mg/kg/day PCNB with 11% HCB, but none at 250 mg/kg/day. Insufficient details provided; inadequate data. Supplementary.

TERATOGENICITY, RABBIT

**057 074793, "Developmental Toxicity Study in New Zealand White Rabbits." (Keller, K.A., IRDC, study 399-070, 6/24/88). PCNB, Lot MDD 080687, 97.3% (0.025% HCB), was administered by oral gavage to groups of 16 artificially inseminated New Zealand White rabbits at dose levels of 0 (0.2% high viscosity CMC vehicle control), 12.5, 125, or 250 mg/kg/day on days 7 through 19 of gestation. An additional study was conducted at dose levels of 0 (vehicle control), 6.25, or 125 mg/kg/day. Reduced food consumption and maternal weight along with increased resorptions and decreased mean fetal weight was noted at 250 mg/kg/day. The fetal effects are considered secondary to the maternal toxicity. There was no evidence of teratogenicity. Maternal NOEL = 125 mg/kg/day (decreased food consumption and weight gain); Developmental NOEL = 125 mg/kg/day (increased resorptions and decreased fetal weight). The study is ACCEPTABLE, and no adverse developmental health effect is noted (J. Kishiyama and G. Chernoff, 9/25/90). 057 074792, Range-Finding Study for 074793.

GENE MUTATION

014 915714, "Mutagenesis Induced in Mutant Strains of Salmonella typhimurium by Pesticides", (Pesticide Research Laboratory, Pennsylvania State University, # 3517, 8/30/77). PCNB, 98% purity, at 0, 1, 5, 25, 125, or 325 µg/plate in the Ames plate test for histidine reversion with Salmonella typhimurium strains TA-98, TA-100, TA-1535, TA-1537, and TA-1538, with/without S9 rat liver (Aroclor induced) activation. **Adverse effects** (increase in revertants with TA1535 and activation) reported. UNACCEPTABLE, (no details of test procedure or results). (Remsen, 5/13/85)

014 915713, "Evaluation of Selected Pesticides as Chemical Mutagens In Vitro and In Vivo Studies", (Stanford Research Institute, Menlo Park, CA., # 3544, May 1977).

Salmonella typhimurium, PCNB technical 99% purity at 5, 10, 50, 100, 500, or 1000 µg/plate in the Ames test for histidine reversion with Salmonella typhimurium strains TA100, TA1535, TA1537, and TA1538 with/without S9 mouse liver (Aroclor induced) activation. Insufficient information for assessment; UNACCEPTABLE, not upgradeable (TA98 not used, inadequate concentration tested, no toxicity data, no replicate plate values). (Remsen, 5/13/85).

028 029676, Summary of 014 915713 (Salmonella typhimurium).

014 915713, "Evaluation of Selected Pesticides as Chemical Mutagens In Vitro and In Vivo Studies", (Stanford Research Institute, Menlo Park, CA., # 3544, May 1977).

Escherichia coli, PCNB technical, 99% purity, at 1, 10, 50, 100, 500, or 1000 ug/plate in the plate assay for tryptophane forward/reverse mutation with Escherichia coli strains WP2, W3110, and p3478 with/without S9 mouse liver (Aroclor induced) activation. Insufficient information for evaluation. UNACCEPTABLE, not upgradeable (inadequate description of test and results, no justification for maximum level tested). (Remsen, 5/13/85)

038 060488, "Mutagenicity of PCNB in Salmonella typhimurium." (NTP TR325, 1/87). PCNB in DMSO at 0, 100, 333, 1000, 3,333, 6,667 µg/plate was tested with and without S9 fraction from induced liver of rat and hamster in TA100, TA1535, TA1537, and TA98 in the plate test; no adverse effects indicated in tabulated data. UNACCEPTABLE, not upgradeable (summary of data only; full report required). (Harnois, 10/6/87)

038 060489-90, "Mutagenicity of PCNB in L5178Y/TK^{+/-} Mouse Lymphoma Cells", (NTP TR325, 1/87). PCNB in acetone at 1.25, 2.5, 5.0, 7.5, and 10.0 ug/ml was tested without S9 or with rat liver S9. No adverse effects indicated in tabulated data. UNACCEPTABLE, not upgradeable (summary of data only, full report required). (Harnois, 10/6/87).

Although no one study is acceptable to close the data gap, a review of

the data on file showed that there was sufficient information to allow a scientific evaluation. The overall indication is that the test substance was negative for gene mutation effect both with and without activation. Harnois, 10/87.

CHROMOSOME EFFECTS

**014 915713, "Evaluation of Selected Pesticides as Chemical Mutagens In Vitro and In Vivo Studies", (Stanford Research Institute, Menlo Park, CA., # 3544, May 1977). PCNB technical, 99% purity, administered in the diet of ICR/SIM mice for 7 weeks to 20 males/level; mated with 40 females/level for 8 weekly periods; 0, 1250, 2500, or 5000 mg/kg/day. TEM as positive control. No adverse effects (dominant lethal) reported. NOEL \geq 5000 mg/kg/day. ACCEPTABLE (Remsen, 5/13/85).

028 029678, summary of 014 915713 (dominant-lethal, mouse).

038 060492, "Induction of Chromosomal Aberrations in Chinese Hamster Ovary Cells by PCNB", (NTP TR325, 1/87). PCNB in DMSO at 2.4, 7.5, 24.0, and 75.0 ug/ml was tested without S9 for 8-10 hrs and harvested 2-3 hrs later; with S9 (rat liver, induced) for 2 hrs and harvested 8-10 hrs later. **Adverse effects** reported: (increased % cells with abnormalities without S9 at \geq 7.5 ug/ml; elevated % at all levels with S9, marked elevation at 75 μ g/ml; NOT ACCEPTABLE, not upgradeable (summary of data only; full report required). (Harnois, 10/6/87)

The data gap is closed. The positive findings in the CHO cultures represent the effect of the test substance under conditions of definite exposure and sampling of all cells exposed. The negative results in the in vivo assay indicate that the test substance and/or its metabolites produced no observed effect on the cells in the testes (Harnois, 10/87).

DNA DAMAGE

**014 915713, "Evaluation of Selected Pesticides as Chemical Mutagens In and In Vivo Studies", (Stanford Research Institute, Menlo Park, CA., # 3544, May 1977). PCNB technical, 99% purity, in DMSO added to confluent WI38 cell cultures at 0, 10^{-7} , 10^{-6} , 10^{-5} , 10^{-4} , or

10^{-3} M (no activation, 3 hrs exposure) or at 0, 10^{-5} , 10^{-4} , or 10^{-3} M (with activation, 1 hr exposure). Precipitate at 10^{-3} M. After incubation with [3 H]-thymidine, DNA was extracted and counts taken by LSC. No adverse effect reported. ACCEPTABLE. (Remsen, 5/13/85)

038 060491, "Induction of Sister-Chromatid Exchanges in CHO Cells by PCNB", (NTP, TR325, 1/87). PCNB in DMSO at 0.75, 2.4 and 7.5 μ g/ml was tested without and with induced rat liver S9. No adverse effects indicated in tabulated data. UNACCEPTABLE, not upgradeable. (Summary report of data only; full report required.) (Harnois, 10/6/87)

The data gap is closed; two types of test indicative of DNA repair were negative. Harnois, 10/87.

NEUROTOXICITY

(Not required at this time)

ADDITIONAL INFORMATION

036 050840, "Study of Pesticide Genotoxicity", (SRI International, Menlo Park, CA., published in Basic Life Sciences, volume 21, pg. 275-326, 1982, Waters, M.D., et al), (Summary of genetic testing). Summary results are given for PCNB (various lots) in several types of gene mutation, chromosome, and DNA damage assays. No adverse results were reported. Supplemental.