MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Pentachloronitrobenzene (CAS # 82-68-8)

FROM: Robert Sills, AQD Toxics Unit Supervisor

SUBJECT: Pentachloronitrobenzene ITSL change in the averaging time from 24 hrs to annual

DATE: December 23, 2015

The current ITSL for Pentachloronitrobenzene (11 ug/m^3) was derived on May 30, 2006 (see attached justification memo). The averaging time (AT) assigned to the ITSL at that time was 24 hours, as per the default methodology at that time (Rule 232(2)(b)). The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is being changed from 24 hours to annual at this time.

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for pentachloronitrobenzene (CAS #82-68-8)

FROM: Anne Kim, Air Quality Division, Toxics Unit

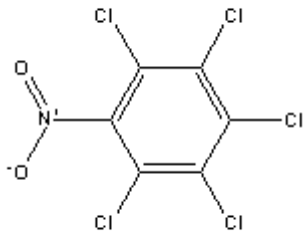
SUBJECT: Screening Level Derivation

DATE: May 30, 2006

The initial threshold screening level (ITSL) for pentachloronitrobenzene (PCNB) is 11 µg/m³ based on a 24-hour averaging time.

The following references or databases were searched to identify data to determine the screening level: U.S. Environmental Protection Agency (EPA) Integrated Risk Information System, Registry for Toxic Effects of Chemical Substances, American Conference of Governmental and Industrial Hygienists Threshold Limit Values, National Institute for Occupational Safety and Health Pocket Guide to Hazardous Chemicals, Environmental Protection Bureau Library, International Agency for Research on Cancer Monographs, Chemical Abstract Service (CAS) - Online (1967 – 2006), National Library of Medicine, Health Effects Assessment Summary Tables, and National Toxicology Program Status Report. The EPA has not established a reference concentration or reference dose for PCNB. The molecular weight of PCNB is 295.3 g. The molecular structure of PCNB is shown in Figure 1.

Figure 1



This compound was initially evaluated by AQD staff in 1993 using interim procedures to derive an impact of 5 ug/m^3 and 10.5 ug/m^3 with an 8-hour and 24-hour averaging time, respectively. PCNB was then again reviewed in 2003, and a screening level of 11 ug/m^3 based on a 24-hour averaging time was proposed. This chemical is being re-reviewed to finalize an ITSL for PCNB.

Background

PCNB is a solid that can range in color from white to yellow depending on its purity. This insoluble substance has a musty odor. PCNB is a fungicide applied to soil for a number of vegetables (e.g., cabbage, beans, broccoli, potatoes, and tomatoes), ornamental crops (e.g., azaleas, carnations, grasses, lilies, and roses), agricultural field crops (e.g., cotton and soybeans), and one fruit (e.g., bananas), and is a fungicide applied to seeds (e.g., barley, corn, cotton, oats, rice, and wheat).

PCNB became commercially important in the United States in the early 1960s. Humans can potentially be exposed to PCNB via the oral route by ingesting foods that have PCNB residues, especially oil and fat. Occupational exposure to PCNB is also possible via the dermal route for workers involved in producing pesticides and for agricultural workers involved in applying PCNB to soils and seeds. (NCI, 1978; WHO, 1987; NTP, 1987).

Animal Toxicity

In a study conducted by Finnegan et al. (1958, secondary reference), groups of seven albino rats of each sex were exposed via the diet at concentrations of 0, 63.5, 635, 1250, 2500, or 5000 ppm PCNB for three months. Both male and female rats exposed to 5000 ppm and the male rats exposed to 2500 ppm showed a decrease in growth and survival rates. Except the female rats in the 63.5 ppm dose group, all PCNB-treated groups showed liver hypertrophy. Rats receiving the highest dose showed fine vacuolization of liver cell cytoplasm. There were no observed hematological changes.

Finnegan et al. (1958, secondary reference) also conducted a two-year study in rats. Groups of 10 rats of each sex were exposed to 0, 25, 100, 300, 1000, or 2500 ppm PCNB in the diet. This commercial preparation was only 20% pure PCNB. Blood tests resulted in no hematological changes. Growth depression, however, was observed in rats exposed to concentrations of 100 ppm and above.

A one-year study in mongrel dogs was conducted by Finnegan et al (1958, secondary reference). Each group consisting of three dogs were fed diets containing 25, 200, or 1000 ppm PCNB. Neither body weights nor survival rates were adversely affected, and no hematological changes were observed. A non-dose-dependent change in histopathology was noted by the enlargement of liver cells.

A two-year study reported by FAO/WHO (1970, secondary reference) exposed groups of three dogs of each sex to 0, 500, 1000, or 5000 ppm PCNB. A dose-dependent change in the liver was observed in all treated dogs with the most severe damage occurring in the highest dose group, showing fibrosis, constriction of hepatic cell cords, decreased size of the periportal areas, and leukocyte infiltration. Similar adverse effects, but to a lesser extent, were seen in the 1000 and 500 ppm dose groups. Other effects observed in the 5000 ppm treated dogs included decreased hematopoiesis and atrophy of the bone marrow.

A study conducted by Borzelleca et al. (1971) reported effects of PCNB exposure to purebred beagle dogs for two years. Groups of four dogs of each sex were fed diets containing 0, 5, 30, 180, or 1080 ppm. Dose-related changes were not seen upon urine analyses, blood chemistry tests, or observations of mortality, body weight, food consumption and estrous cycles. Interestingly, decreased hematocrit values were seen

in male dogs exposed to 30 and 180 ppm PCNB at 18 months but not in dogs exposed to 1080 ppm PCNB. The dogs exposed to 1080 ppm PCNB did, however, show higher liver weight values, and histological examinations showed reversible hepatic and renal changes. This reversible histological change was also seen in the 180 ppm dose group.

A study in rhesus monkeys was performed by Kogel et al. (1979). Two male and two female monkeys were orally exposed to 2 ppm PCNB in the diet for 70 days. Nothing remarkable became apparent upon exposure; the histopathology, clinical chemistry, and serum cortisol levels were all within normal limits.

Human Toxicity

There is very little information available on the effects of PCNB exposure in humans. Only one reference to an occupational worker contracting conjunctivitis has been reported (WHO, 1984).

Teratogenicity

A study conducted by Courtney et al. (1976, secondary reference) observed renal agenesis in fetuses given 500 ppm technical PCNB (87% purity), but found no effect after administering pure PCNB (99% purity).

Berkowitz et al. (1976, secondary reference) found that PCNB was not teratogenic in AKR mice after exposing them up to 500 ppm.

Carcinogenicity

In a screening study, Innes et al. (1969) studied the carcinogenic effect of PCNB exposure to mice. A concentration of 464 ppm PCNB was given by stomach tube daily from the age of seven days to 28 days. For the next 78 weeks, a diet feed containing 1206 ppm PCNB was given to the mice. The results showed increased incidence of hepatomas over control. All other tumors found in the exposure groups occurred at comparable rates to control.

An NCI study (1978) reported the results of a carcinogenicity bioassay on groups of 50 Osborne-Mendel rats of each sex and 50 B6C3F1 mice of each sex. Each group was exposed to PCNB (97% purity with 12 impurities) via their diet for 78 weeks. The time-weighted average dietary concentrations of PCNB were 5417 and 10064 ppm for male rats, 7875 and 14635 ppm for female rats, 2606 and 5213 ppm for male mice, and 4093 and 8187 ppm for female mice. Twenty animals of each species and each sex fed the basal diet served as controls. After the 78 weeks of exposure, additional observation of the rats continued for 33-35 weeks and for 14-15 weeks for the mice. With no appearance of any statistically significant or biologically significant increased incidences of tumors occurring in the exposed animals compared to the untreated control animals, the report concluded that PCNB was not carcinogenic in either the Osborne-Mendel rats or the B6C3F1 mice.

Discussion

The positive teratogenicity and carcinogenicity results from PCNB exposure is generally accepted in the scientific community to be caused by the presence of the impurity of hexachlorobenzene, which is a known teratogen and carcinogen.

The study conducted by Borzelleca and colleagues (1971) was the critical study used by EPA and ACGIH to derive a RfD of 0.003 mg/kg/day and a TLV of 0.5 mg/m^3, respectively – the critical effect being liver toxicity (IRIS, 2006; ACGIH, 1992). All studies mentioned above that looked at the liver as an endpoint found a PCNB-related effect in the liver. This supports the use of Borzelleca et al.'s study results to derive an ITSL, and because EPA used this same study to set a RfD, the RfD will be used to derive the ITSL for PCNB. This is in accordance to Rule 232(1)(b).

Derivation of Screening Level

ITSL = RfD x (70 kg)/(20 m^3)
>where RfD = Reference Dose

ITSL = 0.003 mg/kg x (70 kg)/(20 m^3)

ITSL = 0.0105 mg/m^3

ITSL = 10.5 ug/m^3 = **11 ug/m^3**

Therefore, the ITSL for PCNB (82-68-8) is 11 ug/m^3 based on a 24-hour averaging time.

References

American Council of Governmental Industrial Hygienists (ACGIH). 1992. Documentation of the Threshold Limit Values and Biological Exposure Indices. 6th Ed revised. pp 1172-1176.

Berkowitz, J., Stevens, J., Arnold, D., Goyer, M., Senechal, D., Harrison, J., Ludwig, R., and Newmeyer, J. 1976. Substitute Chemical Program: Initial Scientific Review of PCNB. United States Environmental Protection Agency, Office of Pesticide Programs, Criteria and Evaluation Division. Washington D.C. 20460. EPA/540/1-75-016. In: World Health Organization (WHO). 1984. Environmental Health Criteria 41. Quintozene. Geneva, Switzerland. ISBN 92-4-154181-4; 41(0). 38p.

Borzelleca, J.F., Larson, P.S., Crawford, E.M., Hennigar, G.R., Kuchar, E.J., and Klein, H.H. 1971. Toxicologic and Metabolic Studies on Pentachloronitrobenzene. *Toxicology and Applied Pharmacology*. 18: 522 – 534.

Courtney, K.D., Copeland, M.F., and Robbins, A. 1976. The Effects of PCNB, Hexachlorobenzene and Related Compounds on Fetal Development. *Toxicol. Appl. Pharmacol.* 35: 239 – 256. In: World Health Organization (WHO). 1984. Environmental Health Criteria 41. Quintozene. Geneva, Switzerland. ISBN 92-4-154181-4; 41(0). 38p.

FAO/WHO. 1970. 1969 Evaluations of Some Pesticide Residues in Foods. Rome. Food and Agriculture Organization of the United Nations. In: World Health Organization (WHO). 1984. Environmental Health Criteria 41. Quintozene. Geneva, Switzerland. ISBN 92-4-154181-4; 41(0). 38p.

Finnegan, J.K., Larson, P.S., Smith, R.B., Haag, H.B., and Hennigar, G.R. 1958. Acute and Chronic Toxicity Studies on Pentachloronitrobenzene. *Arch. Int. Pharmacodyn.* 114: 38 – 52. In: World Health Organization (WHO). 1984. Environmental Health Criteria 41. Quintozene. Geneva, Switzerland. ISBN 92-4-154181-4; 41(0). 38p.

Innes, J.R.M., Ulland, B.M., Petrucelli, L., Fishbein, L., Hart, E.R., Pallotta, A.J., Bates, R.R., Falk, H.L., Gart, J.J., Klein, M., Mitchell, I., and Peters, J. 1969. Bioassay of Pesticides and Industrial Chemicals for Tumorigenicity in Mice: A Preliminary Note. *J. Nat. Cancer Inst*. 42: 1101 – 1114.

IRIS. 2006. Pentachloronitrobenzene (PCNB) CASRN 82-68-8. Integrated Risk Information System. http://www.epa.gov/iris/search.htm.

Kogel, W., Muller, W.F., Coulston, F., and Korte, F.J. 1979. Fate and Effects of Pentachloronitrobenzene in Rhesus Monkeys. *Agric. Food. Chem*. 27(6): 1181 – 1185.

National Cancer Institute (NCI). 1978. Bioassay of Pentachloronitrobenzene for Possible Carcinogenicity (CAS NO. 82-68-8). *NCI Technical Report Series* No. 61. NCI-CG-TR-61.

National Toxicology Program (NTP). Jan 1987. Toxicology and Carcinogenesis Studies of Pentachloronitrobenzene (CAS NO. 82-68-8) in B6C3F1 Mice (Feed Studies). *NTP Technical Report Series* No. 325.

World Health Organization (WHO). 1984. Environmental Health Criteria 41. Quintozene. Geneva, Switzerland. ISBN 92-4-154181-4; 41(0). 38p.