

## APPENDIX A

### ATSDR MINIMAL RISK LEVEL AND WORKSHEETS

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) [42 U.S.C. 9601 et seq.], as amended by the Superfund Amendments and Reauthorization Act (SARA) [Pub. L. 99-499], requires that the Agency for Toxic Substances and Disease Registry (ATSDR) develop jointly with the U.S. Environmental Protection Agency (EPA), in order of priority, a list of hazardous substances most commonly found at facilities on the CERCLA National Priorities List (NPL); prepare toxicological profiles for each substance included on the priority list of hazardous substances; and assure the initiation of a research program to fill identified data needs associated with the substances.

The toxicological profiles include an examination, summary, and interpretation of available toxicological information and epidemiologic evaluations of a hazardous substance. During the development of toxicological profiles, Minimal Risk Levels (MRLs) are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure. MRLs are based on noncancer health effects only and are not based on a consideration of cancer effects. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the no-observed-adverse-effect level/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (365 days and longer) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive chemical-induced end point considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

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MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as a hundredfold below levels that have been shown to be nontoxic in laboratory animals.

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology, expert panel peer reviews, and agencywide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published levels. For additional information regarding MRLs, please contact the Division of Toxicology, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road, Mailstop E-29, Atlanta, Georgia 30333.

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: PCBs  
CAS Number: 11097-69-1  
Date: September 2000  
Profile Status: Final  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 87k  
Species: Monkey

Minimal Risk Level: 0.03  µg/kg/day  ppm

Reference: Rice 1997, 1998, 1999b; Rice and Hayward 1997, 1999a

Experimental design: A series of studies were conducted that investigated effects of postnatal exposure to a PCB congener mixture, representing 80% of the congeners present in breast milk in Canadian women, on learning in monkeys. Groups of five and eight male monkeys were orally administered doses of 0 or 0.0075 mg/kg/day, respectively, from birth to 20 weeks of age. The daily dose was divided into thirds and administered prior to the first three daily feedings via syringe to the back of the mouth. The dose level represents the approximate daily intake of a nursing human infant whose mother's milk contained 50 ppb PCBs (the Health Canada guideline for maximum concentration in breast milk). At the end of the dosing period (i.e., at 20 weeks of age), the levels of PCBs in fat and blood in the treated monkeys were 1.7–3.5 ppm and 1.84–2.84 ppb, respectively. Corresponding values in the control monkeys were 0.05–0.20 ppm and 0.30–0.37 ppb. Beginning at 3 years of age, the monkeys were tested on a series of nonspatial discrimination reversal problems followed by a spatial delayed alternation task. Additional testing was done at 4.5 and 5 years of age.

Effects noted in study and corresponding doses: Treated monkeys showed decreased median response latencies and variable increases in mean response latencies across three tasks of nonspatial discrimination reversal. There was no difference in overall accuracy of the tests or correlation between performance and tissue levels of PCBs. Treated monkeys also displayed retarded acquisition of a delayed alternation task and increased errors at short delay task responses. These findings were interpreted as a learning/performance decrement rather than an effect on memory *per se*. In a separate portion of this study (Rice 1997), treated monkeys displayed shorter mean interresponse times when compared with controls. The increase in pause time for fixed-interval performance emerged more slowly across 48 sessions in treated monkeys. For fixed-ratio performance tasks, the control monkeys decreased their mean pause time across 10 sessions, whereas the treated monkeys did not. Rice (1997) interpreted these results as suggesting learning deficit, perseveration, and/or inability to inhibit inappropriate responding as a result of postnatal PCB exposure. Testing of these monkeys at 4.5–5 years of age showed that treated animals performed in a less efficient manner than controls under a differential reinforcement of low rate (DRL) schedule of reinforcement (Rice 1998). There were no differences between groups on the accuracy of performance on a series of spatial discrimination reversal tasks, although some treated monkeys made more errors than others on certain parts of the experiment. Further tests conducted at about 5 years of age did not find treatment-related effects on a series of concurrent RI-RI (random interval) schedules of reinforcement (Rice and Hayward 1999a). This schedule was designed to study behavior in transition (learning) as well as at steady state. However, there was a difference between treated and control monkeys on performance on a progressive ratio (PR) schedule. Rice and Hayward (1999a) stated that this finding may be indicative of retarded acquisition of the steady-state PR performance in treated monkeys.

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Dose and end point used for MRL derivation: The tested dose level, 0.0075 mg/kg/day, is a less serious LOAEL for neurobehavioral toxicity. This LOAEL is a particularly appropriate basis for MRL derivation due to the human relevance of the tested PCB mixture (a congener mixture analogous to that in human breast milk), dose level (approximate daily intake of a nursing human infant whose mother's milk contained 50 ppb PCBs), and resulting PCB tissue and blood levels (near background concentrations found in the general human population). Support for the LOAEL is provided by the occurrence of minimal immunological alterations in the same monkeys at 0.0075 mg/kg/day (Arnold et al. 1999), as well as clinical signs of toxicity (ocular and dermal changes) and decreased antibody responses in offspring of monkeys that were exposed to a similar dose level of Aroclor 1254 (0.005 mg/kg/day) for approximately 46 weeks during gestation and nursing (Arnold et al. 1995); these studies are summarized below in the other pertinent information section.

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 3 for extrapolation from animals to humans
- 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

The monkeys that were evaluated for neurodevelopmental toxicity by Rice and coworkers were also tested for other kinds of effects earlier in life (Arnold et al. 1999). Following exposure to 0.0075 mg/kg/day of the simulated human milk congener mixture during the first 20 weeks of life, the monkeys were periodically examined for the following endpoints for at least the following 46 weeks: bone development (at birth); general health status; formula intake; food and water consumption; body weight; tooth eruption; somatic measurements; and hematology, serum biochemistry, and immunology indices. Immunological assessment of the infants was started at 22 weeks of age and included IgM and IgG antibody production following immunization with SRBC, lymphoproliferative activity of peripheral leucocytes in response to mitogens (PHA, ConA, and PWM), numbers of peripheral leucocytes and their subsets, and NK cell activity. Few statistically significant changes were observed in any of the monitored parameters. Anti-SRBC titers were reduced in the treated monkeys but not significantly different from controls. Absolute mean numbers of B lymphocytes were significantly lower in treated monkeys (no change in mean percent), but the effect was transient because it was not observed when re-evaluated in the monkeys at 1 year of age. The investigators concluded that, overall, the effects on the infant immune system were mild and of unclear biological significance due to large inter-animal variability related to small numbers of animals.

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In another study (Arnold et al. 1995), oral exposure of adult female monkeys for approximately 44 months (total exposure; pre-conception, gestation, and lactation) to a similarly low dose (0.005 mg/kg/day) of an Aroclor PCB mixture resulted in immunological and dermal/ocular effects in their offspring. Groups of 16 female Rhesus monkeys self-ingested capsules containing Aroclor 1254 in a glycerol/corn oil mixture (1:1) in doses of 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/day. After 25 months of exposure, approximately 90% of the animals had attained an apparent pharmacokinetic steady state with respect to adipose concentrations of PCBs. After 37 months of exposure, the females were mated with untreated males, and dosing was continued throughout breeding and gestation and into the first part of the lactation period. Maternal treatment was discontinued when the infants were 7 weeks old (to preclude ingestion of the mother's dosing capsule) and resumed after the infants were weaned at age 22 weeks. Mothers were dosed with PCBs for 37 months prior to mating, and infants born to these mothers were exposed for a duration of approximately 46 weeks (average 24 weeks gestation plus 22 weeks nursing). Study end points included numbers of impregnations, live infants, postpartum deaths, abortions, suspected resorptions, stillbirths, and gestation length. On the day of parturition all infants were x-rayed to ascertain osseous development. Body weight, clinical health, hematology, and serum biochemistry were periodically evaluated in the infants and maternal animals during the lactation period, and subsequently in the dams until the infants were 78 weeks old and in the infants until they were 122 weeks old. The offspring were also evaluated for changes in tooth eruption and anthropometric measurements throughout the study, and immunological changes when they were 20 and 60 weeks old. Four immunological tests were performed: IgM and IgG antibodies to SRBC; lymphocyte proliferation response to PHA, ConA, and PWM mitogens; mixed lymphocyte culture assay (one-way); and natural killer cell activity. Most of the control and all treated offspring were autopsied at 122 weeks of age.

PCB-related effects were induced in the adult monkeys and their offspring (Arnold et al. 1995). Conception rate was significantly reduced at 0.02 mg/kg/day and higher doses. Because this effect occurred in the adult animals that were mated after 37 months of exposure, 0.02 mg/kg/day is a serious LOAEL for reproductive toxicity for chronic-duration exposure. Exposure during gestation and lactation resulted in both fetal toxicity and postnatal effects in the offspring. Fetal mortality was increased at 0.02 mg/kg/day and higher doses. Incidence rates for fetal mortality (combined abortions, suspected resorptions, and stillbirths) were 2/11, 5/10, 3/4, 2/6, and 4/5 in impregnated monkeys in the 0, 0.005, 0.02, 0.04, and 0.08 mg/kg/day groups, respectively, and displayed a significant increasing dose-related trend ( $p=0.040$ ). Statistical comparison of the treated and control groups showed that the fetal mortality incidence rates were increased at 0.02 mg/kg/day ( $p=0.077$ ) and significantly increased at 0.08 mg/kg/day ( $p=0.036$ ). The precision of this statistical comparison is limited by the small numbers of animals, which obscures the high response rate in the 0.02 mg/kg/day group (i.e., that there were 3 fetal deaths in 4 impregnated animals, and that the combined incidence of fetal and neonatal deaths was 4/4). Evaluation of the offspring, limited by the small numbers of surviving animals, showed mild clinical manifestations of PCB exposure and some immunological test differences at 0.005 and 0.04 mg/kg/day (no infants survived beyond postpartum week 2 in the other dose groups). The major clinical signs in the surviving exposed offspring were inflammation and/or enlargement of the tarsal (Meibomian) gland, nail lesions, and gum recession. For example, in the control, 0.005, and 0.04 mg/kg/day dose groups, incidences of tarsal gland inflammation and/or enlargement were 1/9, 4/4, and 3/3; incidences of nail bed prominence were 0/9, 3/4, and 3/3; incidences of elevated nails were 0/9, 2/4, and 2/3; incidences of nails folding on themselves were 0/9, 1/4, and 3/3; and incidences of gum recession were 0/9, 1/4, and 2/3. Immunological alterations in the exposed offspring mainly included suppressed antibody responses to SRBC. IgM antibody levels to SRBCs were significantly reduced in comparison to controls at 0.005 and 0.04 mg/kg/day at week 22 ( $p=0.056$  and  $0.023$ , respectively) and week 23 ( $p=0.043$  and  $0.029$ , respectively), and at 0.005 mg/kg/day at weeks 61, 62, and 63 ( $p=0.028$ ,  $0.043$ , and  $0.056$ , respectively). IgM titers were also suppressed at 0.04 mg/kg/day during weeks 61, 62, and 63, but statistical significance was precluded by the small number of infants ( $n=2$ ) in this group. Other immunological changes included significantly reduced mitogen (ConA)-induced lymphocyte proliferation compared to

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controls at 0.04 mg/kg/day at weeks 28 and 60 ( $p=0.036$  and  $0.053$ , respectively). Although evaluation of the offspring data is complicated by the small number of animals, it is highly relevant that the clinical and immunological effects in the infants are similar to those observed in their chronically exposed dams at the same dose levels as low as 0.005 mg/kg/day (Arnold et al. 1993a, 1993b; Tryphonas et al. 1989, 1991a, 1991b). The effects on the dams are detailed in the in the worksheet for the chronic oral MRL.

Evidence that the 0.0075 mg/kg/day less serious LOAEL is an appropriate dose level for intermediate-duration MRL derivation is provided by the observation that the next highest tested dose level in monkeys (or any other species) is 0.02 mg/kg/day (Arnold et al. 1995), which is a serious LOAEL for fetal mortality as indicated above.

Agency Contact (Chemical Manager): Obaid Faroon

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**MINIMAL RISK LEVEL (MRL) WORKSHEET**

Chemical Name: PCBs  
CAS Number: 11097-69-1  
Date: September 2000  
Profile Status: Final  
Route:  Inhalation  Oral  
Duration:  Acute  Intermediate  Chronic  
Key to Figure: 148k  
Species: Monkey

Minimal Risk Level: 0.02  µg/kg/day  ppm

Reference: Tryphonas et al. 1989, 1991a

Experimental design: (human study details or strain, number of animals per exposure/control groups, sex, dose administration details):

Groups of 16 female Rhesus monkeys self-ingested capsules containing Aroclor 1254 in a glycerol/corn oil mixture (1:1) in doses of 0, 0.005, 0.02, 0.04, or 0.08 mg/kg/day. The monkeys were challenged with injected sheep red blood cells (SRBC) at 23 months of exposure and received a secondary challenge with SRBC at 55 months. The animals had achieved an apparent pharmacokinetic steady state at 23 months based on PCB concentrations in blood and fat. End points examined at 23 months (Tryphonas et al. 1989) included: antibody titers (IgG and IgM) to SRBC, lymphocyte transformation in response to two mitogens (PHA and ConA), quantitation of T- and B-lymphocytes, total serum immunoglobulin levels (IgG, IgM, and IgA), serum proteins, and serum hydrocortisone level. End points examined at 55 months (Tryphonas et al. 1991a, 1991b) included: body weights, IgM and IgG titers in response to secondary immunization with SRBC, lymphocyte proliferation in response to three mitogens (PHA, ConA, and PWM), mix lymphocyte culture assay, phagocytic activity of peripheral blood monocytes following stimulation with phorbol myristate acetate (PMA) or Zymosan, interleukin 1 production in response to *E. coli*, lymphocyte subpopulation analysis, antibody response to pneumococcus antigens, serum hydrocortisone level, serum complement activity, natural killer cell activity, levels of serum thymosins, interferon production by Con A-stimulated leukocytes, and tumor necrosis factor production. As indicated below in the other pertinent information section, clinical health findings (Arnold et al. 1993a) and reproduction and offspring findings (Arnold et al. 1995) were also reported for the monkeys that were tested for immunotoxicity.

Effects noted in study and corresponding doses:

IgM (all doses except 0.02 mg/kg/day) and IgG (all doses) antibody levels to SRBC were significantly reduced compared to controls after 23 months, although no clear dose-response relationships were observed (Tryphonas et al. 1989). Secondary challenge with SRBC after 55 months showed decreasing dose-related trends in the IgM and IgG anamnestic responses, although only IgM was significantly lower than controls at all dose levels (Tryphonas et al. 1991a). Other immunologic changes included alterations in lymphocyte T-cell subsets characterized by a significantly decreased ratio of T-inducer/helper (CD4) cells to T-cytotoxic/suppressor (CD8) cells, due to reduced CD4 and increased CD8 cells, at 0.08 mg/kg/day (not tested at lower doses) after 23 months. No effects on total lymphocytes or B-cells were found, indicating that T-cells were preferentially affected by the PCBs, although there were no exposure-related changes in T-cell subsets after 55 months suggesting that adaptation had occurred. Statistically significant dose-related trends, but no significant differences between exposed and control

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groups, were observed after 55 months for decreasing lymphocyte proliferation in response to mitogens (PHA and ConA, but not PWM), increasing NK cell activity, increasing levels of serum thymosin alpha-1, decreasing phagocytic activity of peripheral blood monocytes following activation with PMA, and increasing total serum complement activity.

Dose and end point used for MRL derivation: The lowest dose level tested, 0.005 mg/kg/day, is a LOAEL for decreased antibody response. Interpretation of the adversity of this effect is complicated by a lack of data on immunocompetence and the essentially inconclusive findings in the other tested end points; however, support for the 0.005 mg/kg/day LOAEL is provided by mild clinical manifestations of toxicity at the same dose. As indicated below in the other pertinent information section, eyelid and toe/finger nail changes were observed in some monkeys at doses as low as 0.005 mg/kg/day (Arnold et al. 1993a).

NOAEL  LOAEL

Uncertainty Factors used in MRL derivation:

- 10 for use of a LOAEL
- 3 for extrapolation from animals to humans
- 10 for human variability

Was a conversion factor used from ppm in food or water to a mg/body weight dose?

No

If an inhalation study in animals, list conversion factors used in determining human equivalent dose:

NA

Was a conversion used from intermittent to continuous exposure?

No

Other additional studies or pertinent information that lend support to this MRL:

No other studies investigated immunological effects of chronic exposure to PCBs. Intermediate-duration studies, however, have conclusively shown that oral exposure to commercial PCB mixtures can induce morphological and functional alterations in the immune system of rats, mice, guinea pigs, and monkeys. Effects in the non-primate species occurred at relatively high doses (generally 4 mg/kg/day) and included decreased thymus and spleen weights in rats, mice, and guinea pigs exposed to Aroclors 1260, 1254, or 1248 (Allen and Abrahamson 1973; Bonnyns and Bastomsky 1976; Smialowicz et al. 1989; Street and Sharma 1975; Vos and Van Driel-Grootenhuis 1972); reduced antibody responses to tetanus toxoid in guinea pigs exposed to Clopen A-60, keyhole limpet hemocyanin in rats exposed to Aroclor 1254, and SRBC in mice exposed to Aroclor 1242 (Exon et al. 1985; Loose et al. 1977, 1978a, 1978b, 1979; Vos and Van Driel-Grootenhuis 1972); increased susceptibility to infection by Moloney leukemia virus in mice exposed to Aroclor 1254 or 1242, herpes simplex virus in mice exposed to Kanechlor 500, and bacterial endotoxin and malarial parasite in mice exposed to Aroclor 1242 (Imanishi et al. 1980; Koller 1977; Loose et al. 1979); reduced skin reactivity to tuberculin in guinea pigs exposed to Clopen A-60 (Vos and Van Driel-Grootenhuis 1972); and reduced NK cell activity in rats exposed to Aroclor 1254 (Smialowicz et al. 1989; Talcott et al. 1985).



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Intermediate-duration oral studies of Aroclors in monkeys confirm the observations of PCB immunotoxicity in rats, mice, and guinea pigs, indicate that non-human primates are more sensitive than the other species, and support the findings of the chronic immunotoxicity study in monkeys (Tryphonas et al. 1989, 1991a, 1991b) used as the basis of the chronic oral MRL. Results of intermediate-duration studies in monkeys included decreased antibody responses to SRBC, increased susceptibility to bacterial infections, and/or histopathological changes in the thymus, spleen, and lymph nodes in adult monkeys and their offspring at 0.1–0.2 mg/kg/day doses of Aroclor 1254 and 1248 (Abrahamson and Allen 1973; Allen and Barsotti 1976; Allen et al. 1980; Barsotti et al. 1976; Thomas and Hinsdill 1978; Truelove et al. 1982; Tryphonas et al. 1986a). Additionally, results of studies in infant monkeys are consistent with the data in adults showing immunosuppressive effects of Aroclor 1254 at doses as low as 0.005 mg/kg/day. Evaluation of *in utero* and lactationally exposed offspring from the monkeys in the Tryphonas et al. (1989, 1991a, 1991b) studies indicated exposure-related reductions in IgM antibody levels to SRBC and mitogen-induced lymphocyte transformation that paralleled the findings in the maternal animals (Arnold et al. 1995).

Support for the chronic LOAEL of 0.005 mg/kg/day is provided by clinical observations on the same monkeys that were immunologically evaluated by Tryphonas et al. (1989, 1991a, 1991b). Examinations of the monkeys exposed to 0.005–0.08 mg/kg/day Aroclor 1254 during the first 37 months of the study showed characteristic dose-related ocular and dermal effects, including eye exudate, inflammation and/or prominence of the tarsal (Meibomian) glands, and various finger and toe nail changes (Arnold et al. 1993a). Statistical analyses found significant increasing dose-related trends in incidence rates, total frequency of observed occurrences and/or onset times for these effects, with some treated and control group comparisons showing significant differences at doses as low as 0.005 mg/kg/day. Effects that were significantly increased in the 0.005 mg/kg/day group included increased total frequencies of inflamed and/or prominent tarsal glands, toenail separations, and elevated toenails. Additionally, monkeys from this study that were mated after 37 months of exposure and continued to be exposed to 0.005 mg/kg/day Aroclor 1254 through gestation and lactation had offspring with clear clinical signs of PCB intoxication, manifested as inflammation and/or enlargement of the tarsal glands, nail lesions, and gum recession (Arnold et al. 1995). Further, the next highest dose level in this study (0.02 mg/kg/day) is a chronic serious LOAEL for reproductive toxicity (reduced conception rate) (Arnold et al. 1995). Conception rate, adjusted for the total number of matings, was significantly lower than controls at 0.02, 0.04, and 0.08 mg/kg/day ( $p=0.009$ ,  $0.039$ , and  $0.005$ , respectively), but not at 0.005 mg/kg/day ( $p=0.085$ ). Similar results were noted after adjustment for the number of matings with positive sires. There was a significant ( $p=0.017$ ) decrease in conception rate with increasing dose with both types of mating adjustments. Percentages of impregnations (number impregnated/number available) in the 0, 0.005, 0.02, 0.04, and 0.08 mg/kg/day groups were 69, 63, 27, 43, and 33%, respectively. The 0.02 mg/kg/day doses in this study are also serious effect levels for developmental toxicity (fetal mortality), as discussed in the worksheet for the intermediate-duration oral MRL.

Agency Contact (Chemical Manager): Obaid Faroon

**Table A-1. PCB Concentrations in Blood and Breast Milk in Epidemiology Studies**

Study	Mean PCB concentrations		Basis of analysis	Health effects
	Blood (wet basis)	Breast milk (lipid basis)		
Michigan Mother-Child Study (Fein et al. 1984a, 1984b; Jacobson and Jacobson 1996a, 1997; Jacobson et al. 1984a, 1985, 1990a, 1990b, 1992)	maternal serum: 6.1 ppb (fish eaters) 4.1 ppb (nonfish eaters)  cord serum: 2.0 ppb	866 ppb (fish eaters) 622 ppb (nonfish eaters)	total PCBs	Exposure from consumption of contaminated sportfish (Lake Michigan). Reduced birth weight, head circumference and gestational age in newborns, neurobehavioral alterations in newborn and older children <sup>a</sup> .
Oswego Newborn and Infant Development Project (Lonky et al. 1996; Stewart et al. 1999, 2000a)	cord blood: 0.8 ppb (fish eaters) <sup>b</sup> 1.03 ppb (nonfish eaters)	NR <sup>c</sup>	total PCBs (68 congeners)	Exposure from consumption of contaminated sportfish (Lake Ontario). Neurobehavioral alterations in newborn children <sup>d</sup> .
Wives of Swedish Fisherman Cohort Study (Rylander et al. 1995, 1998b)	maternal serum: 1.0 ppb (median, fish eaters) 0.92 ppb (median, nonfish eaters)	NR	PCB 153	Exposure from consumption of fatty fish (Baltic Sea). Increased risk of low birth weight was associated with increasing maternal serum levels of PCB 153 (300–400 ppb).
Lake Michigan Aging Population Study (Schantz et al. 1996a, 1999)	adult serum: 16.0 ppb (fish eaters) 6.2 ppb (nonfish eaters)	NR	total PCBs	Exposure from consumption of contaminated sportfish (Lake Michigan). No significant effects on visual-motor coordination and hand steadiness tests in adults.
New York State Angler Cohort Study (Buck et al. 1997, 1999, 2000; Kostyniak et al. 1999; Mendola et al. 1995a, 1997)	NR <sup>a</sup>	NR	NA	Exposure from consumption of contaminated sportfish (Lake Ontario). Assessments of female and male reproductive endpoints found indications of fish consumption-related reductions in menstrual cycle length and female fecundability.

Table A-1. PCB Concentrations in Blood and Breast Milk in Epidemiology Studies (*continued*)

Study	Mean PCB concentrations		Basis of analysis	Health effects
	Blood (wet basis)	Breast milk (lipid basis)		
Michigan Anglers Cohort Study (Courval et al. 1999)	NR <sup>e</sup>	NR	NA	Exposure from consumption of contaminated sportfish (Lake Erie, Lake Huron, or Lake Michigan). Associations between conception delay and fish consumption were found in exposed men but not their wives.
Inuit Infant Study (Dewailly et al. 2000)	NR	621 ppb	∑ 3 non-dioxin-like congeners (PCBs 138, 153, and 180)	Exposure from consumption of arctic sea mammal fat and other marine foods. Some immunologic alterations were associated with exposure to PCBs as well as other organochlorine compounds <sup>f</sup> .
North Carolina Breast Milk and Formula Project (Gladen et al. 1988; Longnecker et al. 2000; Rogan and Gladen 1991, 1992; Rogan et al. 1986a, 1986b, 1987)	maternal serum: 9.06 ppb (median)  cord serum: <4.27 ppb (median)	1.8 ppm <sup>g</sup>	total PCBs	General population exposure. Neurobehavioral alterations in infants <sup>h</sup> . No associations between PCBs and birth weight, head circumference, or thyroid hormones.

Table A-1. PCB Concentrations in Blood and Breast Milk in Epidemiology Studies (*continued*)

Study	Mean PCB concentrations		Basis of analysis	Health effects
	Blood (wet basis)	Breast milk (lipid basis)		
Dutch Mother-Child Study (Huisman et al. 1995a, 1995b; Koopman-Esseboom et al. 1994a, 1994b, 1996; Lanting et al. 1998c; Patandin et al. 1999; Weisglas- Kuperus et al. 1995)	NR	620 ppb	total PCBs (26 congeners including 118, 138, 153, and 180)	General population exposure. Reduced birth weight. Reduced growth (weight, length, and head circumference) during first 3 months in formula-fed, but not breast-fed, children. Neurobehavioral alterations and changes in T-lymphocyte subpopulations and thyroid hormone levels in infants <sup>1</sup> .
	maternal plasma: 2.2 ppb	430 ppb	$\Sigma$ 4 non-dioxin-like congeners (PCBs 118, 138, 153, and 180)	
	cord plasma: 0.45 ppb	25.6 ppb	$\Sigma$ 3 dioxin-like congeners (PCBs 77, 126, and 169)	
	child plasma: 0.75 ppb (median, breast-fed at 42 months) 0.21 ppb (median, formula-fed at 42 months)	0.16 ppb TEQ  0.046 ppb TEQ	$\Sigma$ 3 dioxin-like congeners and 17 PCDD and PCDF 2,3,7,8-substituted congeners	
European Background PCB Study — German Sample (Winneke et al. 1998b)	cord plasma: 0.55 ppb	427 ppb	$\Sigma$ 3 non-dioxin-like congeners (PCBs 138, 153, and 180)	General population exposure. Neurodevelopmental and thyroid hormone alterations in infants <sup>1</sup> .

**Table A-1. PCB Concentrations in Blood and Breast Milk in Epidemiology Studies (continued)**

Study	Mean PCB concentrations		Basis of analysis	Health effects
	Blood (wet basis)	Breast milk (lipid basis)		

<sup>a</sup> Newborn children from mothers who ate contaminated fish were more likely to exhibit hypoactive reflexes, more motor immaturity, poorer lability of states, and greater amount of startle. Testing at 4 years of age found that prenatal exposure was associated with poorer performance on the Verbal and the Memory scales of the McCarthy Scales of Children's Abilities, as well as less efficient visual discrimination processing and more errors in short-term memory scanning. Evaluation of the children at 11 years of age showed that prenatal exposure was significantly associated with lower full-scale and verbal IQ scores and poorer reading word comprehension.

<sup>b</sup> Although the concentration of total PCBs did not differ between fish eaters and controls, both the proportion (mol %) and absolute concentration (ppb) of the most heavily chlorinated PCB congeners (C17-C19) were markedly elevated in the cord blood of the fish eaters compared to the controls. PCB congeners of light (C11-C13) or moderate (C14-C16) chlorination were unrelated to fish consumption. The most heavily chlorinated congeners in cord blood were also the only congeners that correlated with breast milk levels.

<sup>c</sup> Actual values of PCBs in milk were not reported. The C17-C19 congeners in breast milk and cord blood were correlated while no correlation was found for the lightly (C11-C13) or moderately (C14-C16) chlorinated congeners.

<sup>d</sup> Children born to mothers with high consumption of contaminated fish had a greater number of abnormal reflexes and less mature autonomic responses than newborns from low-fish eaters or nonfish eaters. Heavily chlorinated congeners (C17-C19) were associated with poorer Habituation and Autonomic scores.

<sup>e</sup> Exposure was assessed using an index developed to estimate cumulative lifetime PCB exposure through fish consumption.

<sup>f</sup> Associations between increasing levels of organochlorine compounds in breast milk and risk of acute otitis media during the first year of life were found, although the data are insufficient for identifying whether the effect may be due to PCBs, hexachlorobenzene, *p,p'*-DDE, or other chemicals. No statistically significant changes in immunological indices were observed, although there were indications of reduced total serum IgA levels and altered T-lymphocyte subpopulations in breast-fed Inuit infants at 7 and 12 months of age.

<sup>g</sup> Average PCB levels in milk at birth. In lactating women, the levels declined about 20% over 6 months and about 40% over 18 months.

<sup>h</sup> Higher PCB levels were associated with less muscle tone and activity and hyporeflexia. Prenatal exposure to PCBs (levels in milk at birth) was associated with a significant decrease in PDI scores at the ages of 6 and 12 months.

<sup>i</sup> Prenatal exposure to PCBs (cord blood) was not significantly associated with either PDI or MDI scores at 7 months of age. Postnatal exposure was significantly associated with lower PDI scores, but not MDI scores. Cognitive abilities evaluated in these children at 42 months of age using the KABC showed a significant decreased performance associated with prenatal exposure to PCBs. PCB and CDD TEQs in maternal plasma during pregnancy were compared with thyroid T<sub>3</sub>, T<sub>4</sub>, and TSH concentrations in cord plasma at delivery and in the venous plasma of infants at ages 2 weeks and 3 months. Hormone levels were negatively correlated with CDD TEQs, PCB TEQs, and combined CDD and PCB TEQs, at all ages.

<sup>j</sup> Prenatal exposure was not significantly associated with MDI or PDI scores at 7 months of age. Postnatal exposure was significantly associated with lower MDI scores, but not with PDI scores. A positive correlation was found between serum concentrations of thyroid TSH and total PCBs in infants.

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	93 (no CI)	Latency <10 year	Brown and Jones 1981
						108 (no CI)	Latency 10<20 year	
						60 (no CI)	Latency >20 year	
						89 (95% CI= 63–122)	Overall SMR; further analysis revealed that risk was not related to employment duration. Analyses of mortality from cancers at various specific sites did not show statistically significantly increased risk <sup>a</sup> .	
	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	78 (no CI)	Overall SMR; update of Brown and Jones (1981) study; seven additional years' follow-up. Analyses of mortality from cancers at various specific sites did not show statistically significantly increased risk <sup>b</sup> .	Brown 1987b

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Capacitor manufacturing plant workers in New York State exposed $\geq 90$ days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly elevated SMRs	Analyses for mortality from all cancers combined were stratified in the following ways: (1) hourly versus salaried compensation schedule, and gender of worker (analyses were also conducted for various cancer sites <sup>c</sup> ); (2) gender, employment duration, and latency. Only "limited" exposure to other chemicals was reported.	Kimbrough et al. 1999a
	Swedish capacitor manufacturing male workers employed $\geq 6$ months versus Swedish national rates	142	1965–1982	1965–1978 (mean exposure 6.5 years)	RR	1.30 (95% CI= 0.52–2.67)	Median latency time =13 years	Gustavsson et al. 1986

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Swedish capacitor manufacturing male workers employed $\geq 6$ months versus Swedish national rates	242	1965–1991	1965–1978	SMR	No statistically significantly elevated SMRs	Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for mortality by all cancers combined were conducted for the entire cohort or stratified by exposure status (low versus high exposure). SMR=133 (95% CI=76–216) for the entire cohort. Analyses of mortality from cancers at various sites did not show statistically significantly increased risk <sup>d</sup> .	Gustavsson and Hogstedt 1997
	Italian capacitor manufacturing workers employed $\geq 1$ week versus national mortality rates	2,110 (544 males and 1,556 females)	1946–1982	1946–1978	SMR	Males: 253 (95% CI=144–415) Females: 156 (no CI; not statistically significant)	In a follow-up study that considered nine additional years of latency (Tironi et al. 1996), mortality from all cancers was not statistically significantly increased in males (SMR=109; CI=67–168) or females (SMR=118; CI=71–184).	Bertazzi et al. 1987
	Italian capacitor manufacturing workers employed $\geq 1$ week versus local mortality rates	2,110 (544 males and 1,556 females)	1946–1982	1946–1978	SMR	Males: 183 (95% CI=104–300) Females: 226 (95% CI=123–385)	NC	Bertazzi et al. 1987



**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (continued)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Japanese <i>Yusho</i> food PCB contamination registrants versus national death rates	887 males	1968–1983	1968 (poisoning incident)	SMR	2.13 (no CI; p<0.01)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. SMR was not statistically significant in an evaluation of 874 females. Average follow-up was approximately 11 years. Analyses of mortality from cancers at various sites did not show statistically significantly increased risk <sup>e</sup> .	Kuratsune et al. 1987
	Taiwanese <i>Yu-Cheng</i> food PCB contamination victims versus national mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	Males: SMR=0.69 (95% CI=0.3–1.36) Females: SMR=0.4 (95% CI=0.08–1.18) Total: SMR=0.58 (95% CI=0.29–1.04)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. Similarly statistically non-significant findings were obtained in comparisons against local reference populations. Analyses of mortality from cancers at various specific sites did not show statistically significantly increased risk <sup>f</sup> .	Hsieh et al. 1996
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 men and 858 women)	1957–1986	1957–1977	SMR	0.8 (95% CI=0.6–1.1)	Analyses of mortality from cancers at various specific sites did not show statistically significantly increased risk <sup>g</sup> .	Sinks et al. 1992

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (continued)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.84 (95% CI= 0.68–1.03)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents. Analyses of mortality from cancers at various specific sites also did not show statistically significantly increased risk <sup>h</sup> .	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	3.05 (95% CI= 0.99–7.13)	Statistically significant SMR was for squamous cell carcinomas; a statistically non-significant SMR was obtained for melanomas. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer mortality	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race)	138,905	1950–1988	1950–1986	SMR	0.86 (95% CI= 0.84–0.89)	Analyses of mortality from cancers at various specific sites also did not show statistically significant increased risk <sup>1</sup> . Possible confounding factors include co-exposures to solvents, wood preservatives, sunlight, and magnetic fields (which was associated with mortality from brain cancer in this cohort).	Loomis et al. 1997
	Canadian transformer manufacturing plant male workers employed for ≥1 month versus Canadian general male population	2,222	1947–1989	1947–1975	SMR	1.21 (95% CI= 0.90–1.60)	Analysis combined deaths from “definite”, “probable”, and “possible” cancer link. Analysis of “definite” cancer mortality cases yielded an SMR of 0.81 (95% CI=0.57–1.13). Statistically non-significant SMRs were also obtained in all workers employed ≥6 months (n=812) and in transformer assembly workers employed for ≥6 months (n=308). The authors noted that “considerably more exposure” to mineral oils occurred than exposure to PCB-containing askarol transformer fluids.	Yassi et al. 1994

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer incidence	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	142	1965–1982	1965–1978 (mean exposure 6.5 years)	RR	0.92 (95% CI= 0.37–1.90)	Median latency time =13 years	Gustavsson et al. 1986
	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SIR	1.02 (95% CI= 0.88–1.17)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents. Analyses of cancer incidence at various specific sites also did not show statistically significant increased risk <sup>1</sup> .	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Total cancer incidence	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SIR	0.95 (95% CI= 0.89–1.01)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SIR	No statistically significantly elevated SIRs	Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for all cancers were conducted for the entire cohort, for the subgroup with time since first exposure >10 years, and for the high exposure group. Analysis of cancer incidence at various specific sites also did not show statistically significant increases <sup>k</sup> .	Gustavsson and Hogstedt 1997
Liver-related cancer mortality	Capacitor ^ workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	667 (no CI)	Latency <10 years	Brown and Jones 1981
						233 (no CI)	Latency 10–20 years	
						no deaths	Latency >20 years	
						280 (95% CI= 58–820)	Overall value; further analysis revealed that risk not related to employment duration	

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	263 (no CI, $p < 0.05$ )	Overall value; update of Brown and Jones (1981) study; seven additional years' follow-up; no increase in risk with increasing duration of latency or employment. Five cases observed versus 1.9 expected. One liver cancer was metastatic, not primary; when exclude that case, SMR=210 ( $p \geq 0.05$ ) (Nicholson and Landrigan 1994).	Brown 1987b
	Capacitor manufacturing plant workers in New York State exposed $\geq 90$ days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly versus salaried compensation. Male hourly (80; CI=10–289; two deaths); female hourly (89; CI=11–321; two deaths); male salaried (79; CI=2–439; one death); female salaried (no deaths).	Kimbrough et al. 1999a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Swedish capacitor manufacturing male workers employed $\geq 6$ months versus Swedish national rates	242	1965–1991	1965–1978	SMR	No statistically significantly elevated SMRs	Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for mortality by liver cancer were conducted for the entire cohort or stratified by exposure status (low versus high exposure). Only one death due to liver cancer was reported, in the high exposure group. SMRs were 667 (CI=16–3,710) and 196 (CI=5–1,090) for the high exposure group and entire cohort, respectively.	Gustavsson and Hogstedt 1997

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Japanese <i>Yusho</i> food PCB contamination registrants versus national and local death rates	887 males	1968–1983	1968 (poisoning incident)	SMR	5.59 (no CI; $p < 0.01$ )	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. Average follow-up was approximately 11 years. An SMR of 3.85 for males was also statistically significantly elevated ( $p < 0.01$ ; no CI); compared to a local reference population that had an underlying high incidence of liver cancer mortality. Evaluating only those liver cancers in males that were observed after 9 years of latency compared to the local reference population resulted in an SMR of 3.85 ( $p < 0.05$ ; no CI); SMRs were not statistically significant in evaluations of 874 females.	Kuratsune et al. 1987



**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Taiwanese <i>Yu-Cheng</i> food PCB contamination victims versus national mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	Males: 0.29 (95% CI= 0.01–1.62); Females: 1.08 (95% CI= 0.03–6.02)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. One male death and one female death observed. The analysis considered deaths from liver and intrahepatic bile duct cancers combined. Similarly statistically non-significant findings were reported in males and females using a local reference population.	Hsieh et al. 1996
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	1.1 (95% CI= 0.0–6.4)	NC	Sinks et al. 1992

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer mortality	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.48 (95% CI= 0.01–2.65)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	0.9 (95% CI= 0.41–1.7)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Liver-related cancer incidence	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.73 (95% CI=0.57–0.93)	The analysis included combined mortalities from cancers of the liver, biliary passages, and gall bladder. An additional analysis of liver (not specified) cancer mortality yielded an SMR of 0.79 (95% CI=0.55-1.1)	Loomis et al. 1997
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SIR	No statistically significantly elevated SIRs	Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for incidence of liver and bile duct cancer were conducted for the entire cohort or stratified by exposure status (low versus high exposure) or time since first exposure (>10 or >20 years). SIR=256 (95% CI=31-926) for the entire cohort. One each of cholangiocellular cancer and adenocarcinoma were reported.	Gustavsson and Hogstedt 1997

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Rectal cancer mortality	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	No deaths	Latency <10 years	Brown and Jones 1981
						417 (no CI)	Latency 10–20 years	
						556 (no CI)	Latency >20 years	
						335 (95% CI= 92–860)	Overall value; an analysis stratified by employment location and sex of worker revealed that observed mortality (3) statistically significantly greater ( $p < 0.05$ ) than expected (0.5) for females in one of two locations (Plant 2) resulting in an SMR of 600 (no CI; 3 observed deaths, 0.5 expected). An SMR of 323 (no CI; 1 observed death, 0.31 expected) was reported in males from plant 1. No deaths from rectum cancer were observed in females in plant 1 or males in plant 2. Analysis by employment duration revealed statistically significantly increased SMR only in the group exposed for 10–14 years (not for longer or shorter durations) in one or both locations, although the number of deaths was small.	

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Rectal cancer mortality	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	211 (no CI; $p \geq 0.05$ )	Overall value; update of Brown and Jones (1981) study; seven additional years' follow-up. Four observed deaths versus 1.9 expected. For females in plant 2 (previously statistically significant in Brown and Jones, 1981) the observed/expected mortality ratio was 3/0.8 ( $p \geq 0.05$ ).	Brown 1987b
	Capacitor manufacturing plant workers in New York State exposed $\geq 90$ days vs. U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly vs. salaried compensation. A statistically non-significant SMR of 169 (95% CI=46–434; 4 observed deaths, 2.3 expected) was reported in female hourly workers.	Kimbrough et al. 1999a
	Japanese <i>Yusho</i> food PCB contamination registrants versus national death rates	1,761 (887 males, 874 females)	1968–1983	1968 (poisoning incident)	SMR	Males: 1.60 (no CI; $p > 0.05$ ) Females: no deaths	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis combined cancers of the rectum, sigmoid colon, and anus. One observed death. Average follow-up was approximately 11 years.	Kuratsune et al. 1987

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Rectal cancer mortality	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 male, 858 female)	1957–1986	1957–1977	SMR	0.8 (95% CI= 0.0–4.5)	NC	Sinks et al. 1992
	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.73 (95% CI= 0.2–1.86)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	1.02 (95% CI= 0.7–1.46)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Rectal cancer mortality	U.S. male utility workers employed full time for $\geq 6$ months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.79 (95% CI= 0.65–0.95)	NC	Loomis et al. 1997
Respiratory-related cancer mortality	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	88 (95% CI= 35–181)	Overall SMR value	Brown and Jones 1981
	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	59 (no CI)	Overall SMR value; update of Brown and Jones (1981) study; seven additional years' follow-up	Brown 1987b
	Japanese <i>Yusho</i> food PCB contamination registrants versus national death rates	887 males	1968–1983	1968 (poisoning incident)	SMR	3.26 (no CI; $p < 0.01$ )	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis combined cancers of the lung, trachea, and bronchus. SMR was not statistically significant in an evaluation of 874 females. Average follow-up was approximately 11 years.	Kuratsune et al. 1987

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Respiratory-related cancer mortality	Taiwanese <i>Yu-Cheng</i> food PCB contamination victims versus Taiwan national mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	Males: 0.85 (95% CI= 0.10–3.07); Females: 0.88 (95%CI= 0.02–4.91)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis considered deaths from trachea, bronchus, and lung cancers combined. One death in males and one death in females observed. Similarly statistically non-significant findings were reported in males and females using a local reference population.	Hsieh et al. 1996
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 women)	1957–1986	1957–1977	SMR	0.7 (95% CI= 0.4–1.2)	NC	Sinks et al. 1992



**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Respiratory-related cancer mortality	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.78 (95% CI= 0.46–1.28)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	0.86 (95% CI= 0.68–1.07)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Respiratory-related cancer mortality	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.91 (95% CI=0.87–0.95)	The analysis included combined mortalities from cancers of the trachea, bronchus, and lung.	Loomis et al. 1997
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SMR	No statistically significantly elevated SMRs	The analysis focused on mortality from lung cancer. Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses were conducted for the entire cohort or stratified by exposure status (low versus high exposure). SMRs were 152 (CI=31–444), 222 (27–803), and 173 (CI=56–406) for the low and high exposure groups and entire cohort, respectively. A total of five lung cancer mortalities were observed.	Gustavsson and Hogstedt 1997

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Respiratory-related cancer mortality	Canadian transformer manufacturing plant male workers employed for ≥6 months versus Canadian general male population	819	1947–1989	1947–1975	SMR	0.79 (95% CI= 0.26–1.85)	A statistically non-significant SMR was also obtained in transformer assembly workers employed for ≥6 months (n=308). The authors noted that "considerably more exposure" to mineral oils occurred than exposure to PCB-containing askarol transformer fluids.	Yassi et al. 1994
Pancreatic cancer mortality	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	53 (no CI)	One death observed; overall SMR value.	Brown and Jones 1981
	Capacitor workers exposed ≥3 months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	54 (no CI)	Overall SMR value; update of Brown and Jones (1981) study; seven additional years' follow-up.	Brown 1987b

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Pancreatic cancer mortality	Canadian transformer manufacturing plant male workers employed for ≥6 months versus Canadian general male population	2,222	1947–1989	1947–1975	SMR	5.01 (95% CI= 2.50–8.96; 11 observed deaths)	Analysis was for all workers in the transformer plant, with “definite”, “probable”, or “possible” link between death and pancreatic cancer. The “definite” pancreatic cancer mortality cases yielded an SMR of 2.92 (95% CI=1.17–6.01). Among all workers employed for ≥6 months (n=812) an SMR of 7.64 (3.29–15.06) was obtained, and among workers employed for ≥6 months in the transformer assembly department (n=308), an SMR of 12.9 (2.59–37.7) was calculated. The authors noted that “considerably more exposure” to mineral oils occurred than exposure to PCB-containing askarol transformer fluids. Wong (1995) identified other concerns about the positive pancreatic findings, including inclusion of cases that had neither sufficient duration of exposure nor sufficient latency to be related to PCB exposure at the plant.	Yassi et al. 1994

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Pancreatic cancer mortality	Capacitor manufacturing plant workers in New York State exposed $\geq 90$ days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly versus salaried compensation.	Kimbrough et al. 1999a
	Japanese <i>Yusho</i> food PCB contamination registrants versus national death rates	1,761 (887 males, 874 females)	1968–1983	1968 (poisoning incident)	SMR	Males: 1.41 (no CI; $p > 0.05$ ) Females: 2.18 (no CI; $p > 0.05$ )	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. Average follow-up was approximately 11 years. One death in males and one death in females observed	Kuratsune et al. 1987
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	0.7 (95% CI= 0.1–2.5)	NC	Sinks et al. 1992

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Pancreatic cancer mortality	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	0.66 (95% CI= 0.22–1.55)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
Stomach cancer mortality	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	0.84 (95% CI= 0.58–1.18)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Pancreatic cancer mortality	U.S. male utility workers employed full time for $\geq 6$ months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.84 (95% CI= 0.74–0.95)	NC	Loomis et al. 1997
Stomach cancer mortality	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	60 (no CI)	Overall SMR value; one death observed. One observed death, 1.66 expected).	Brown and Jones 1981
	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	36 (no CI)	Overall SMR value; one death observed, update of Brown and Jones (1981) study; seven additional years' follow-up. One observed death, 2.8 expected).	Brown 1987b
	Capacitor manufacturing plant workers in New York State exposed $\geq 90$ days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly versus salaried compensation.	Kimbrough et al. 1999a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Stomach cancer mortality	Japanese <i>Yusho</i> food PCB contamination registrants versus national death rates	1,761 (887 males, 874 females)	1968–1983	1968 (poisoning incident)	SMR	Males: 1.40 (no CI; $p > 0.05$ ) Females: no deaths	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. Average follow-up was approximately 11 years.	Kuratsune et al. 1987
	Taiwanese <i>Yu-Cheng</i> food PCB contamination victims versus Taiwan national and local reference mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	National reference: 0.63 (95% CI= 0.02–3.53) Local reference: 0.65 (95% CI= 0.02–3.59)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis focused on deaths from cancer of the stomach in males. One observed death. No parallel analysis was reported in females.	Hsieh et al. 1996
Stomach cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	1.37 (95% CI= 0.82–2.23)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a



**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Intestinal cancer mortality	Taiwanese <i>Yu-Cheng</i> food PCB contamination victims versus Taiwan national and local reference mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	National: 19.76 (95% CI= 0.5–110.3) Local: 26.46 (95% CI= 0.67–147.4)	Heated PCB-contaminated rice oil also contained PCDFs and other contaminants. The analysis focused on deaths from cancer of the small intestine in males; one observed death. No parallel analysis was reported in females.	Hsieh et al. 1996
	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	99 (95% CI= 27–254)	Overall SMR value.	Brown and Jones 1981
	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	104 (no CI)	Overall SMR value; update of Brown and Jones (1981) study; seven additional years' follow-up.	Brown 1987b
	U.S. male utility workers employed full time for $\geq 6$ months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	0.93 (95% CI= 0.85–1.02)	NC	Loomis et al. 1997

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
"Digestive tract" cancer mortality	Italian capacitor manufacturing male workers employed $\geq 1$ week versus national mortality rates	544 males	1946–1982	1946–1978	SMR	346 (95% CI=141–721)	For this analysis, cancers of the stomach (2), pancreas (2), liver (1), and biliary tract (1) were included by the authors in the "digestive tract" group. A SMR of 274 (95% CI=112-572) was also obtained in males in a comparison against a local reference group. No statistically significant digestive tract SMR was obtained for female workers compared to either national or local reference groups, or in a follow-up evaluation with an additional 9 years of latency (Tironi et al. 1996).	Bertazzi et al. 1987
"Digestive organs" cancer mortality	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	0.6 (95% CI=0.2–1.1)	NC	Sinks et al. 1992

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
"Digestive cancer" mortality	Canadian transformer manufacturing plant male workers employed for $\geq 1$ month versus Canadian general male population	2,222	1947–1989	1947–1975	SMR	1.45 (95% CI=0.85–2.33)	Analysis combined deaths from "definite", "probable", and "possible" cancer link. Analysis of "definite" digestive cancer mortality cases yielded an SMR of 0.85 (95% CI=0.43–1.53; 11 observed deaths). Statistically non-significant SMRs were also obtained in all workers employed $\geq 6$ months (n=812) and in transformer assembly workers employed for $\geq 6$ months (n=308). The authors noted that "considerably more exposure" to mineral oils occurred than exposure to PCB-containing askarol transformer fluids.	Yassi et al. 1994

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Italian capacitor manufacturing female workers employed $\geq 1$ week versus local mortality rates	1,556 females	1946–1982	1946–1978	SMR	377 (95% CI=115–877)	A SMR of 266 (not statistically significant; CI not reported; 4 observed, 1.5 expected) was also obtained in females in a comparison against a national reference group. No statistically significantly elevated hematological cancer SMR was obtained for male workers compared to either local (SMR=263; no CI; 3 observed, 1.1 expected) or national (SMR=375; no CI; 3 observed, 0.8 expected) reference groups.	Bertazzi et al. 1987
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Japanese <i>Yusho</i> food PCB contamination registrants versus national death rates	1,761 (887 males, 874 females).	1968–1983	1968 (poisoning incident)	SMR	Males: 2.23 (no CI; $p > 0.05$ ) Females: no deaths	Heated PCB-contaminated rice oil also contained PCDFS and other contaminants; one observed death in males. The analysis focused on leukemia. Average follow-up was approximately 11 years.	Kuratsune et al. 1987
	Taiwanese <i>Yu-Cheng</i> food PCB contamination victims versus Taiwan national and local mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	National: 61.17 (95% CI=1.55–340.7) Local: 86.45 (95% CI=2.19–481.5)	Heated PCB-contaminated rice oil also contained PCDFS and other contaminants. The analysis focused on Hodgkin's disease in males; no comparable analysis in females was reported. One observed death in males.	Hsieh et al. 1996

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
	Taiwanese <i>Yu-Cheng</i> food PCB contamination victims versus Taiwan national and local mortality rates	1,940 (929 males, 1,011 females)	1979–1991	1979 (poisoning incident)	SMR	National: 7.69 (95% CI= 0.19–42.84) Local: 8.42 (95% CI= 0.21–46.89)	Heated PCB-contaminated rice oil also contained PCDFS and other contaminants. The analysis focused on unspecified leukemia disease in males; comparable analysis in females was not reported. One observed death in males.	Hsieh et al. 1996
	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1976	1940–1976	SMR	46 (no CI)	Lymphatic and hematopoietic cancer mortality; only two deaths; overall SMR value	Brown and Jones 1981
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Capacitor workers exposed $\geq 3$ months versus U.S. white population	2,567	1940–1983	1940–1976	SMR	68 (no CI)	Lymphatic and hematopoietic cancer mortality; overall SMR value; update of Brown and Jones (1981) study; seven additional years' follow-up	Brown 1987b

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	3.08 (95% CI= 1.24–6.35)	The statistically significant SMR was for multiple myeloma. Statistically non-significant SMRs were obtained for Hodgkins and non-Hodgkins lymphoma and for leukemia. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	No statistically significantly increased SMRs	Statistically non-significant SMRs were obtained for Hodgkins and non-Hodgkins lymphomas, multiple myeloma, and leukemia. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a
	U.S. male utility workers employed full time for ≥6 months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	No statistically significant SMRs	Statistically non-significant SMRs were obtained for mortalities from the following hematologic-related cancers: combined neoplasms of the lymphatic and hematopoietic tissues, lymphosarcoma and reticulosarcoma, Hodgkins disease, leukemia and aleukemia, other lymphatic neoplasms.	Loomis et al. 1997

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Swedish capacitor manufacturing male workers employed $\geq 6$ months versus Swedish national rates	242	1965–1991	1965–1978	SMR	No statistically significant SMRs	Statistically non-significant SMRs were obtained for mortalities from the following hematologic-related cancers: combined hematopoietic and lymphatic malignancies, and malignant lymphomas. Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses were conducted for the entire cohort or stratified by exposure status (low vs. high exposure).	Gustavsson and Hogstedt 1997
	Canadian transformer manufacturing plant male workers employed for $\geq 6$ months versus Canadian general male population	819	1947–1989	1947–1975	SMR	No statistically significant SMRs	Statistically non-significant SMRs were obtained in separate analyses for non-Hodgkins lymphomas and leukemias in all workers employed for $\geq 6$ months (n=812) and in transformer assembly workers employed for $\geq 6$ months (n=308). The authors noted that "considerably more exposure" to mineral oils occurred than exposure to PCB-containing askarol transformer fluids.	Yassi et al. 1994



**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer mortality (including lymphatic and hematopoietic cancers)	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	142	1965–1982	1965–1978 (mean exposure 6.5 yrs)	Observed versus expected	1 observed case	The report identified one case of malignant lymphoma, expected number of cases was not reported, but the numbers of deaths from cancers was reported to “correspond well with those expected.” Median latency time=13 years.	Gustavsson et al. 1986
	Capacitor manufacturing plant workers in New York State exposed ≥90 days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly increased SMRs	Analysis stratified by gender and hourly versus salaried compensation. Three separate analyses were conducted for lymphosarcoma, leukemia and aleukemia, and other lymphatic and hematopoietic cancers.	Kimbrough et al. 1999a
	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	1.0 (95% CI= 0.4–2.0)	NC	Sinks et al. 1992

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SIR	No statistically significant SIRs	Statistically non-significant SIRs were obtained for Hodgkins and non-Hodgkins lymphoma, multiple myeloma, lymphatic leukemia, myeloic leukemia, and acute leukemia. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer incidence	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SIR	1.86 (95% CI= 0.96–3.25)	The nearly statistically significant SIR was for acute leukemia. Statistically non-significant SIRs were obtained for Hodgkins and non-Hodgkins lymphoma, multiple myeloma, lymphatic leukemia, and myeloid leukemia. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Hematologic cancer incidence	Swedish capacitor manufacturing male workers employed $\geq 6$ months versus Swedish national rates	242	1965–1991	1965–1978	SIR	No statistically significantly elevated SIRs	Statistically non-significant SIRs were obtained for occurrence of the following hematologic-related cancers: combined hematopoietic and lymphatic malignancies, and non-Hodgkins lymphoma. Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses for all cancers were conducted for the entire cohort, for the subgroup with time since first exposure >10 yrs, and for the high exposure group.	Gustavsson and Hogstedt 1997

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer mortality	Capacitor manufacturing facility workers versus U.S. mortality rates for whites	3,588 (2,785 males, 858 females)	1957–1986	1957–1977	SMR	4.1 (95% CI= 1.8–8.0)	All observed skin cancer deaths (8) were from malignant melanoma, while the expected number of deaths was calculated using mortality rates for basal cell carcinoma, squamous cell carcinoma, and malignant melanoma combined. However, a nested proportional hazards analysis comparing indices of PCB exposure between skin cancer cases and a comparison group showed no relationship between risk of melanoma and cumulative PCB exposure.	Sinks et al. 1992

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer mortality	Capacitor manufacturing plant workers in New York State exposed $\geq 90$ days versus U.S. and regional (surrounding counties) populations	7,075	1946–1993	1946–1977	SMR	No statistically significantly elevated SMRs	The analysis focused on mortality from melanomas. Analyses were stratified by hourly versus salaried compensation schedule, and gender of worker. Only "limited" exposure to other chemicals was reported. There were statistically non-significant increases in melanoma mortality in hourly male workers (SMR=130; 95% CI=42-303; 5 observed deaths, 3.8 expected), hourly female workers (SMR=144; 95% CI=30-421; 3 observed deaths, 2 expected), and salaried male workers (SMR=210; 95% CI=57-538; 4 observed deaths, 1.9 exp).	Kimbrough et al. 1999a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer mortality	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SMR	3.05 (95% CI= 0.99–7.13)	Statistically significant SMR was for squamous cell carcinomas (five cases observed versus 1.6 expected); a statistically non-significant SMR was obtained for melanomas. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a
	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SMR	No deaths observed	Analysis focused on squamous cell skin cancer and melanoma. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer mortality	U.S. male utility workers employed full time for $\geq 6$ months versus U.S. general population mortality rates (adjusted for age, calendar year, and race).	138,905	1950–1988	1950–1986	SMR	1.04 (95% CI=0.86–1.24)	The overall analysis showed no increases in skin cancers. However, an analysis stratified by latency ("lag") and total career exposure showed a positive relationship between adjusted mortality rate ratios (RRs) and cumulative exposure within the group with a lag time of 20 years: 0–2,000 hrs total exposure (RR=1.29 [95% CI=0.76-2.17]), 2,000–10,000 hours (RR=2.56 [95% CI=1.09–5.97]), >10,000 hours [RR=4.81 (95% CI=1.49-15.1)].	Loomis et al. 1997



**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SIR	2.28 (95% CI= 1.45–3.5)	The statistically significant SIR was for squamous cell cancer of the skin. A statistically non-significant SIR was obtained for melanomas. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a
	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SIR	Non-statistically significant SIRs	Statistically non-significant SIRs were obtained for squamous cell cancers and melanomas. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus west coast fishermen	2,896 (east) 8,477 (west)	1965–1988	1968–1988	IRR	1.88 (95% CI= 1.15–3.09)	Exposure duration was not clearly identified. East coast fishermen had higher blood levels of PCBs than the west coast population, but they also had higher levels of dioxins and furans (Svensson et al. 1995b).	Svensson et al. 1995a
	Swedish capacitor manufacturing male workers employed ≥6 months versus Swedish national rates	242	1965–1991	1965–1978	SIR	No observed cases	The analysis focused on malignant melanomas. Update of Gustavsson et al. (1986) study; nine additional years of follow-up. Analyses were conducted for the entire cohort, the high exposure group, and the group with time since first exposure (TSFE) >10 years.	Gustavsson and Hogstedt 1997

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Skin cancer incidence	U.S. male petrochemical plant workers versus National Cancer Survey incidence rates	31	9-year period until late 1950s	9-year period until late 1950s	NR	2 cases observed versus 0.4 expected (p=0.001)	The analysis focused on malignant melanoma. The report was an editorial letter to the journal, indicating that the men were "heavily" exposed to Aroclor 1254. A follow-up letter (Bahn et al. 1977) indicated that the men were R&D workers who were exposed to other chemicals, but another group of 20 R&D workers with less PCB exposure had no cases of malignant melanoma. A letter from Lawrence (1977) indicated that an epoxide scavenger additive to PCBs was found to have a "pronounced carcinogenic effect in a skin painting study in animals, and that the skin cancer may not be from the PCBs, per se.	Bahn et al. (1976)
Lip cancer incidence	Swedish west coast fishermen consuming fish with PCBs versus regional reference populations	8,477	1968–1988	1968–1988	SIR	1.92 (95% CI= 1.29–2.8)	Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. Mercury and selenium were also higher in fishermen than in referents (Svensson et al. 1995b).	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
Lip cancer incidence	Swedish east coast (Baltic Sea) fishermen consuming fish with PCBs versus regional reference populations	2,896	1968–1988	1968–1988	SIR	2.6 (95% CI= 1.05–5.36)	Analysis focused on squamous cell skin cancer and melanoma. Exposure duration was not clearly identified, although fishermen were reported to consume fish at twice the rate of the reference population. East coast fishermen had higher blood levels of PCBs than the reference populations, but they also had higher levels of dioxins and furans (Svensson et al. 1995b); mercury and selenium were also higher in fishermen than in referents.	Svensson et al. 1995a

**Table A-2. Summary of Epidemiological Information Concerning Human PCB Exposures: Retrospective Analysis of Cohort Mortality from Cancer or Cohort Cancer Incidence (*continued*)**

End points	Comparison groups	Number exposed	Study period	Exposure period	Measure of effect	Outcome	Comments	Reference
------------	-------------------	----------------	--------------	-----------------	-------------------	---------	----------	-----------

<sup>a</sup>No statistically significant increase in SMR was obtained in the Brown and Jones (1981) overall analysis for the following cancer sites: stomach, intestine (except rectum), rectum, liver/biliary passages, pancreas, respiratory system, breast, lymphatic/hematopoietic systems, and other cancer.

<sup>b</sup>No statistically significant increase in SMR was obtained in the Brown (1987b) update analysis that was stratified by employment location and gender for the following cancer sites: stomach, intestine (except rectum), pancreas, respiratory, urinary, lymphatic/hematopoietic, breast, female genital organs, and other cancers.

<sup>c</sup>No statistically significant increase in SMR was obtained in the Kimbrough et al. (1999a) analysis that was stratified by gender of worker and hourly versus salaried compensation for the following cancer sites: tongue, buccal cavity, pharynx, esophagus, stomach, intestine, rectum, biliary passages and liver, pancreas, larynx, trachea-bronchus-lung, breast, cervix uteri, uterus, ovary-tube-broad ligament, prostate, kidney, bladder and urinary tract, skin, brain and nervous system, connective tissue, other unspecified cancer, lymphosarcoma, leukemia and aleukemia, other lymphatic and hematopoietic cancer.

<sup>d</sup>No statistically significant increase in SMR was obtained in the Gustavsson and Hogstedt (1997) analysis that was stratified by exposure status for the following cancer sites: esophageal, liver, lung, prostate, bladder, kidney, hematopoietic and lymphatic malignancies, and malignant lymphomas.

<sup>e</sup>No statistically significant increase in SMR was obtained in the Kuratsune et al. (1987) analysis that was stratified by gender for the following cancer sites: esophagus, stomach, rectum-sigmoid colon-anus, pancreas, breast, uterus, and leukemia.

<sup>f</sup>No statistically significant increase in SMR was obtained in the Hsieh et al. (1996) analysis using either national or local reference populations for the following cancer sites: males: nasopharynx, stomach, small intestine, liver and intrahepatic bile ducts, trachea-bronchus-lung, unspecified leukemia; females: liver and intrahepatic bile ducts, trachea-bronchus-lung, and bone.

<sup>g</sup>No statistically significant increase in SMR was obtained in the Sinks et al. (1992) analysis for the following cancer sites: buccal cavity-pharynx, digestive organs, liver-biliary passages-gallbladder, pancreas, rectum, respiratory system, kidney, lymphatic and hematopoietic tissue, and brain and nervous system.

<sup>h</sup>No statistically significant increase in SMR was obtained in the Svensson et al. (1995a) analyses stratified by east coast versus west coast fisherman for the following cancer sites: esophagus, stomach, colon, rectum, liver, pancreas, lung-larynx, breast, prostate, bladder, kidney, brain-nervous system, Hodgkins and non-Hodgkins lymphoma, and leukemia.

<sup>i</sup>No statistically significant increase in SMR was obtained in the Loomis et al. (1997) analyses for the following cancer sites: buccal cavity-pharynx, stomach, intestine, rectum, liver-biliary passages-gall bladder, liver (not specified), pancreas, trachea-bronchus-lung, breast, prostate, kidney, urinary organs, skin, brain and nervous system, lymphatic and hematopoietic systems, lymphosarcoma and reticulosarcoma, Hodgkins disease, leukemia and aleukemia, and other lymphatic neoplasms.

<sup>j</sup>No statistically significant increase in SIR was obtained in the Svensson et al. (1995a) analyses stratified by east coast versus west coast fishermen for the following sites: esophagus, colon, rectum, liver-bile ducts, pancreas, lung-larynx, prostate, renal parenchyma, urinary bladder, brain, soft tissue sarcoma, Hodgkins lymphoma, non-Hodgkins lymphoma, multiple myeloma, lymphatic leukemia, myeloid leukemia, and acute leukemia.

<sup>k</sup>No statistically significant increase in SIR was obtained in the Gustavsson and Hogstedt (1997) analysis conducted for the entire cohort, for the subgroup with time since first exposure >10 years, and for the high exposure group for the following cancer sites: esophageal, liver, larynx, lung, prostate, bladder, malignant melanoma, nervous system, soft tissue sarcoma, hematopoietic-lymphatic, non-Hodgkins lymphoma, and other sites.



## APPENDIX B

### USER'S GUIDE

#### Chapter 1

##### Public Health Statement

This chapter of the profile is a health effects summary written in non-technical language. Its intended audience is the general public especially people living in the vicinity of a hazardous waste site or chemical release. If the Public Health Statement were removed from the rest of the document, it would still communicate to the lay public essential information about the chemical.

The major headings in the Public Health Statement are useful to find specific topics of concern. The topics are written in a question and answer format. The answer to each question includes a sentence that will direct the reader to chapters in the profile that will provide more information on the given topic.

#### Chapter 2

##### Relevance to Public Health

The Relevance to Public Health section provides a health effects summary based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information. This summary is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions.

1. What effects are known to occur in humans?
2. What effects observed in animals are likely to be of concern to humans?
3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

The section covers endpoints in the same order they appear within the Discussion of Health Effects by Route of Exposure section, by route (inhalation, oral, dermal) and within route by effect. Human data are presented first, then animal data. Both are organized by duration (acute, intermediate, chronic). *In vitro* data and data from parenteral routes (intramuscular, intravenous, subcutaneous, etc.) are also considered in this section. If data are located in the scientific literature, a table of genotoxicity information is included.

The carcinogenic potential of the profiled substance is qualitatively evaluated, when appropriate, using existing toxicokinetic, genotoxic, and carcinogenic data. ATSDR does not currently assess cancer potency or perform cancer risk assessments. Minimal risk levels (MRLs) for noncancer end points (if derived) and the end points from which they were derived are indicated and discussed.

Limitations to existing scientific literature that prevent a satisfactory evaluation of the relevance to public health are identified in the Data Needs section.

## APPENDIX B

**Interpretation of Minimal Risk Levels**

Where sufficient toxicologic information is available, we have derived minimal risk levels (MRLs) for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action; but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans. They should help physicians and public health officials determine the safety of a community living near a chemical emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Chapter 2, "Relevance to Public Health," contains basic information known about the substance. Other sections such as 3.9, "Interactions with Other Substances," and 3.10, "Populations that are Unusually Susceptible" provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses for lifetime exposure (RfDs).

To derive an MRL, ATSDR generally selects the most sensitive end point which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest NOAEL that does not exceed any adverse effect levels. When a NOAEL is not available, a LOAEL can be used to derive an MRL, and an uncertainty factor (UF) of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a substance-specific MRL are provided in the footnotes of the LSE Tables.

**Chapter 3****Tables and Figures for Levels of Significant Exposure (LSE)**

Tables (3-1, 3-2, and 3-3) and Figures (3-1 and 3-2) are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species, minimal risk levels (MRLs) to humans for noncancer end points, and EPA's estimated range associated with an upper-bound individual lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. Use the LSE tables and figures for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of No-Observed-Adverse-Effect Levels (NOAELs), Lowest-Observed-Adverse-Effect Levels (LOAELs), or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE Table 3-1 and Figure 3-1 are shown. The numbers in the left column of the legends correspond to the numbers in the example table and figure.



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**LEGEND****See LSE Table 3-1**

- (1) Route of Exposure One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. When sufficient data exists, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure, i.e., inhalation, oral, and dermal (LSE Table 3-1, 3-2, and 3-3, respectively). LSE figures are limited to the inhalation (LSE Figure 3-1) and oral (LSE Figure 3-2) routes. Not all substances will have data on each route of exposure and will not therefore have all five of the tables and figures. The order of the above may change?
- (2) Exposure Period Three exposure periods - acute (less than 15 days), intermediate (15–364 days), and chronic (365 days or more) are presented within each relevant route of exposure. In this example, an inhalation study of intermediate exposure duration is reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.
- (3) Health Effect The major categories of health effects included in LSE tables and figures are death, systemic, immunological, neurological, developmental, reproductive, and cancer. NOAELs and LOAELs can be reported in the tables and figures for all effects but cancer. Systemic effects are further defined in the "System" column of the LSE table (see key number 18).
- (4) Key to Figure Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 18 has been used to derive a NOAEL and a Less Serious LOAEL (also see the 2 "18r" data points in Figure 3-1).
- (5) Species The test species, whether animal or human, are identified in this column. Chapter 2, "Relevance to Public Health," covers the relevance of animal data to human toxicity and Section 3.4, "Toxicokinetics," contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.
- (6) Exposure Frequency/Duration The duration of the study and the weekly and daily exposure regimen are provided in this column. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 18), rats were exposed to toxaphene via inhalation for 6 hours per day, 5 days per week, for 3 weeks. For a more complete review of the dosing regimen refer to the appropriate sections of the text or the original reference paper, i.e., Nitschke et al. 1981.
- (7) System This column further defines the systemic effects. These systems include: respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, and dermal/ocular. "Other" refers to any systemic effect (e.g., a decrease in body weight) not covered in these systems. In the example of key number 18, 1 systemic effect (respiratory) was investigated.
- (8) NOAEL A No-Observed-Adverse-Effect Level (NOAEL) is the highest exposure level at which no harmful effects were seen in the organ system studied. Key number 18 reports a NOAEL of 3 ppm for the respiratory system which was used to derive an intermediate exposure, inhalation MRL of 0.005 ppm (see footnote "b").

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- (9) LOAEL A Lowest-Observed-Adverse-Effect Level (LOAEL) is the lowest dose used in the study that caused a harmful health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. The respiratory effect reported in key number 18 (hyperplasia) is a Less serious LOAEL of 10 ppm. MRLs are not derived from Serious LOAELs.
- (10) Reference The complete reference citation is given in Chapter 8 of the profile.
- (11) CEL A Cancer Effect Level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases.
- (12) Footnotes Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. Footnote "b" indicates the NOAEL of 3 ppm in key number 18 was used to derive an MRL of 0.005 ppm.

**LEGEND****See Figure 3-1**

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

- (13) Exposure Period The same exposure periods appear as in the LSE table. In this example, health effects observed within the intermediate and chronic exposure periods are illustrated.
- (14) Health Effect These are the categories of health effects for which reliable quantitative data exists. The same health effects appear in the LSE table.
- (15) Levels of Exposure concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m<sup>3</sup> or ppm and oral exposure is reported in mg/kg/day.
- (16) NOAEL In this example, 18r NOAEL is the critical endpoint for which an intermediate inhalation exposure MRL is based. As you can see from the LSE figure key, the open-circle symbol indicates to a NOAEL for the test species-rat. The key number 18 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 3 ppm (see entry 18 in the Table) to the MRL of 0.005 ppm (see footnote "b" in the LSE table).
- (17) CEL Key number 38r is 1 of 3 studies for which Cancer Effect Levels were derived. The diamond symbol refers to a Cancer Effect Level for the test species-mouse. The number 38 corresponds to the entry in the LSE table.

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- (18) Estimated Upper-Bound Human Cancer Risk Levels This is the range associated with the upper-bound for lifetime cancer risk of 1 in 10,000 to 1 in 10,000,000. These risk levels are derived from the EPA's Human Health Assessment Group's upper-bound estimates of the slope of the cancer dose response curve at low dose levels ( $q_1^*$ ).
- (19) Key to LSE Figure The Key explains the abbreviations and symbols used in the figure.

# SAMPLE

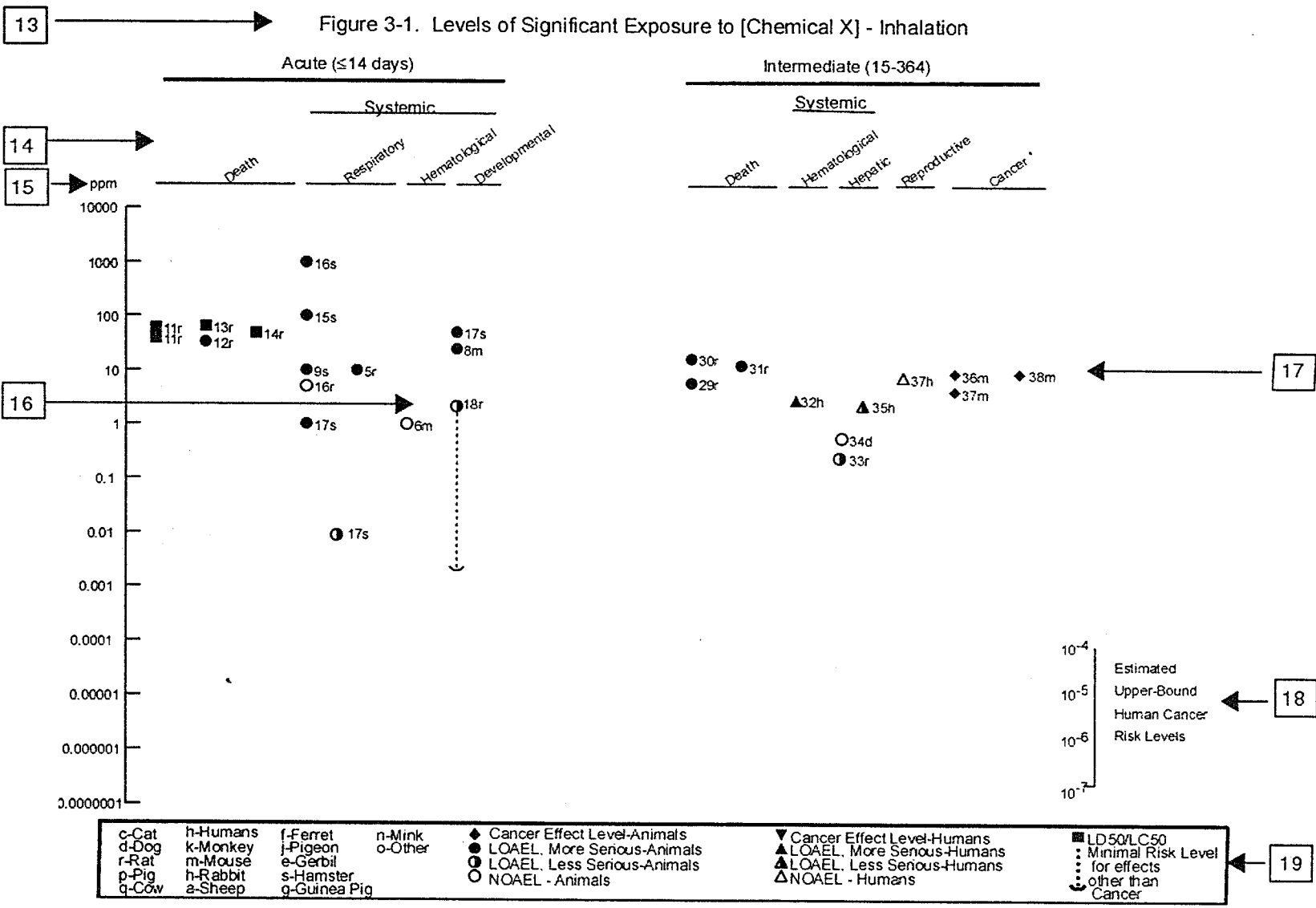
**Table 3-1. Levels of Significant Exposure to [Chemical x] – Inhalation**

Key to figure <sup>a</sup>	Species	Exposure frequency/ duration	System	NOAEL (ppm)	LOAEL (effect)		Reference
					Less serious (ppm)	Serious (ppm)	
<b>INTERMEDIATE EXPOSURE</b>							
	↓	↓	↓	↓	↓		↓
18	Rat	13 wk 5 d/wk 6 hr/d	Resp	3 <sup>b</sup>	10 (hyperplasia)		Nitschke et al. 1981
-----							
<b>CHRONIC EXPOSURE</b>							
						↓	
38	Rat	18 mo 5 d/wk 7 hr/d				20 (CEL, multiple organs)	Wong et al. 1982
39	Rat	89–104 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, nasal tumors)	NTP 1982
40	Mouse	79–103 wk 5 d/wk 6 hr/d				10 (CEL, lung tumors, hemangiosarcomas)	NTP 1982

<sup>a</sup> The number corresponds to entries in Figure 3-1.

<sup>b</sup> Used to derive an intermediate inhalation Minimal Risk Level (MRL) of  $5 \times 10^{-3}$  ppm; dose adjusted for intermittent exposure and divided by an uncertainty factor of 100 (10 for extrapolation from animal to humans, 10 for human variability).

SAMPLE





## APPENDIX C

### ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists
ADI	Acceptable Daily Intake
ADME	Absorption, Distribution, Metabolism, and Excretion
AFID	alkali flame ionization detector
AFOSH	Air Force Office of Safety and Health
AML	acute myeloid leukemia
AOAC	Association of Official Analytical Chemists
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BAT	Best Available Technology
BCF	bioconcentration factor
BEI	Biological Exposure Index
BSC	Board of Scientific Counselors
C	Centigrade
CAA	Clean Air Act
CAG	Cancer Assessment Group of the U.S. Environmental Protection Agency
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	Cancer Effect Level
CELDS	Computer-Environmental Legislative Data System
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CL	ceiling limit value
CLP	Contract Laboratory Program
cm	centimeter
CML	chronic myeloid leukemia
CNS	central nervous system
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
d	day
Derm	dermal
DHEW	Department of Health, Education, and Welfare
DHHS	Department of Health and Human Services
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DOL	Department of Labor
DOT	Department of Transportation
DOT/UN/	Department of Transportation/United Nations/
NA/IMCO	North America/International Maritime Dangerous Goods Code
DWEL	Drinking Water Exposure Level
ECD	electron capture detection
ECG/EKG	electrocardiogram

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EEG	electroencephalogram
EEGL	Emergency Exposure Guidance Level
EPA	Environmental Protection Agency
F	Fahrenheit
F <sub>1</sub>	first-filial generation
FAO	Food and Agricultural Organization of the United Nations
FDA	Food and Drug Administration
FEMA	Federal Emergency Management Agency
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FPD	flame photometric detection
fpm	feet per minute
ft	foot
FR	<i>Federal Register</i>
g	gram
GC	gas chromatography
Gd	gestational day
gen	generation
GLC	gas liquid chromatography
GPC	gel permeation chromatography
HPLC	high-performance liquid chromatography
hr	hour
HRGC	high resolution gas chromatography
HSDB	Hazardous Substance Data Bank
IDLH	Immediately Dangerous to Life and Health
IARC	International Agency for Research on Cancer
ILO	International Labor Organization
in	inch
IRIS	Integrated Risk Information System
K <sub>d</sub>	adsorption ratio
kg	kilogram
kkg	metric ton
K <sub>oc</sub>	organic carbon partition coefficient
K <sub>ow</sub>	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC <sub>Lo</sub>	lethal concentration, low
LC <sub>50</sub>	lethal concentration, 50% kill
LD <sub>Lo</sub>	lethal dose, low
LD <sub>50</sub>	lethal dose, 50% kill
LT <sub>50</sub>	lethal time, 50% kill
LOAEL	lowest-observed-adverse-effect level
LSE	Levels of Significant Exposure
m	meter
MA	<i>trans,trans</i> -muconic acid
MAL	Maximum Allowable Level
mCi	millicurie
MCL	Maximum Contaminant Level
MCLG	Maximum Contaminant Level Goal
mg	milligram
min	minute
mL	milliliter



## APPENDIX C

mm	millimeter
mm Hg	millimeters of mercury
mmol	millimole
mo	month
mppcf	millions of particles per cubic foot
MRL	Minimal Risk Level
MS	mass spectrometry
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NATICH	National Air Toxics Information Clearinghouse
NATO	North Atlantic Treaty Organization
NCE	normochromatic erythrocytes
NCI	National Cancer Institute
NIEHS	National Institute of Environmental Health Sciences
NIOSH	National Institute for Occupational Safety and Health
NIOSHTIC	NIOSH's Computerized Information Retrieval System
NFPA	National Fire Protection Association
ng	nanogram
NLM	National Library of Medicine
nm	nanometer
NHANES	National Health and Nutrition Examination Survey
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NOES	National Occupational Exposure Survey
NOHS	National Occupational Hazard Survey
NPD	nitrogen phosphorus detection
NPDES	National Pollutant Discharge Elimination System
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NSPS	New Source Performance Standards
NTIS	National Technical Information Service
NTP	National Toxicology Program
ODW	Office of Drinking Water, EPA
OERR	Office of Emergency and Remedial Response, EPA
OHM/TADS	Oil and Hazardous Materials/Technical Assistance Data System
OPP	Office of Pesticide Programs, EPA
OPPTS	Office of Prevention, Pesticides and Toxic Substances, EPA
OPPT	Office of Pollution Prevention and Toxics, EPA
OSHA	Occupational Safety and Health Administration
OSW	Office of Solid Waste, EPA
OTS	Office of Toxic Substances
OW	Office of Water
OWRS	Office of Water Regulations and Standards, EPA
PAH	Polycyclic Aromatic Hydrocarbon
PBPD	Physiologically Based Pharmacodynamic
PBPK	Physiologically Based Pharmacokinetic
PCE	polychromatic erythrocytes
PEL	permissible exposure limit
PID	photo ionization detector

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pg	picogram
pmol	picomole
PHS	Public Health Service
PMR	proportionate mortality ratio
ppb	parts per billion
ppm	parts per million
ppt	parts per trillion
PSNS	Pretreatment Standards for New Sources
REL	recommended exposure level/limit
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
RTECS	Registry of Toxic Effects of Chemical Substances
RQ	Reportable Quantity
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
sec	second
SIC	Standard Industrial Classification
SIM	selected ion monitoring
SMCL	Secondary Maximum Contaminant Level
SMR	standard mortality ratio
SNARL	Suggested No Adverse Response Level
SPEGL	Short-Term Public Emergency Guidance Level
STEL	short-term exposure limit
STORET	Storage and Retrieval
TD <sub>50</sub>	toxic dose, 50% specific toxic effect
TLV	threshold limit value
TOC	Total Organic Compound
TPQ	Threshold Planning Quantity
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TRI	Toxics Release Inventory
TWA	time-weighted average
U.S.	United States
UF	uncertainty factor
VOC	Volatile Organic Compound
yr	year
WHO	World Health Organization
wk	week
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer

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$\mu\text{g}$	microgram
$q_1$	cancer slope factor
-	negative
+	positive
(+)	weakly positive result
(-)	weakly negative result



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**APPENDIX E**

**SUMMARY REPORT FOR THE EXPERT PANEL REVIEW  
April 13, 2000**



**SUMMARY REPORT FOR THE EXPERT PANEL REVIEW  
OF THE  
TOXICOLOGICAL PROFILE FOR PCBs**

*Prepared for:*

The Agency for Toxic Substances and Disease Registry  
Division of Toxicology  
Atlanta, Georgia

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**NOTE**

This report was prepared by Eastern Research Group, Inc. (ERG), an ATSDR contractor, as a general record of discussion for the expert panel review meeting on the Toxicological Profile for Polychlorinated Biphenyls. This report captures the main points of scheduled presentations and highlights discussions among the expert panelists. This report does not contain a verbatim transcript of all issues discussed during the meeting. Additionally, the report does not embellish, interpret, or enlarge upon matters that were incomplete or unclear. ATSDR will evaluate the panelists' recommendations and determine what modifications are necessary to the Toxicological Profile. Except as specifically noted, no statements in this report represent analyses or positions of ATSDR or of ERG.



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## APPENDICES

Appendix A—List of Participants

Appendix B—Agenda



**LIST OF ABBREVIATIONS**

ATSDR	Agency for Toxic Substances and Disease Registry
DSA	delayed spatial alteration
EPA	U.S. Environmental Protection Agency
FDA	U.S. Food and Drug Administration
IARC	International Agency for Research on Cancer
ICD	International Classification of Diseases
LOAEL	lowest-observed-adverse-effect level
LSE	levels of significant exposure
MRL	minimal risk level
NHEXAS	National Human Exposure Assessment Survey
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NTP	National Toxicology Program
OECD	Organization for Economic Cooperation and Development
PCBs	polychlorinated biphenyls
TEF	toxic equivalency factor



## EXECUTIVE SUMMARY

A group of expert scientists extensively reviewed the Agency for Toxic Substances and Disease Registry's (ATSDR's) draft Toxicological Profile for Polychlorinated Biphenyls (PCBs), public comments on this profile, and the Agency's proposed disposition of these comments. During a 3-day meeting, the scientists thoroughly discussed and debated the scientific rigor of the toxicological profile and its criticisms. At the end of the meeting, the panelists generally commended ATSDR on its efforts in preparing the draft profile, but they identified numerous areas where the profile should be improved.

Following is a list of the general recommendations that the expert panelists highlighted during their closing statements. An overview of the discussion that led to these recommendations and specific examples of other suggested revisions are documented throughout this report.

- The panelists recommended several improvements to the organization and presentation of the profile. Most importantly, the panelists thought the Health Effects chapter should subordinate information on route of exposure to discussions on endpoints. They also recommended that this chapter of the profile include syntheses of information using a weight-of-evidence approach to develop conclusions. ATSDR agreed to make these and other improvements to the presentation of information in the profile.
- After highlighting several sections of the profile that do not adequately characterize relevant studies, omit studies, or rely too heavily on outdated information, the panelists recommended that ATSDR carefully revise parts of the Health Effects chapter to provide more accurate, balanced, and complete accounts of the past and current information on the public health implications of PCBs.
- On the topic of PCB-related cancer effects, the panelists confirmed that the profile should document carcinogenicity classifications published by the International Agency for Research on Cancer (IARC), the National Toxicology Program (NTP), and the U.S. Environmental Protection Agency (EPA). The panelists also recommended that ATSDR improve its reviews of the occupational epidemiological studies, and compare and contrast their findings.
- The panelists generally agreed that the Tryphonas study is an adequate basis for deriving a chronic oral Minimal Risk Level (MRL), but they strongly recommended that ATSDR consider other studies as a supplemental basis for the final health guidance values. Specifically, panelists thought the human studies of Michigan, North Carolina, and Dutch cohorts might be a supportive basis for

a chronic oral MRL, and they thought an animal study published by Rice might be an adequate basis for an intermediate oral MRL.

- Several panelists thought the profile should offer additional insight into the general population's PCB exposures from fish consumption. They recommended that ATSDR distinguish the potential impacts of consuming fish caught in PCB-contaminated waters from those of consuming fish from supermarkets.

## **1.0 INTRODUCTION**

In December 1998, the Agency for Toxic Substances and Disease Registry (ATSDR) released a draft updated version of the Toxicological Profile for Polychlorinated Biphenyls (PCBs) for public comment. Since then, outside agencies, scientists, special interest groups, and the public have submitted comments on the draft profile. To ensure that ATSDR adequately responds to all comments, and to evaluate the scientific merit of the profile as a whole, the Agency assembled an expert review panel of toxicologists, epidemiologists, environmental health scientists, and other experts on September 27–29, 1999, to review the disposition of comments and critique the toxicological profile itself. This report summarizes the technical discussions of the expert review panel.

### **1.1 Background**

Before releasing a toxicological profile, ATSDR goes through great measures to ensure that the profile accurately reflects the current knowledge base of the science. These measures include various forms of scientific review. For example, every toxicological profile goes through several rounds of internal review at ATSDR (e.g., ATSDR's Intra-Agency Minimal Risk Level Workgroup), external peer review by selected expert scientists, and a public comment period, all before being published in final form. Through this process, expert scientists, special interest groups, the public, and others are all given the opportunity to recommend revisions or additions to ATSDR's toxicological profiles.

The Toxicological Profile for PCBs (Draft for Public Comment) has already been subject to extensive internal and external scientific review. However, given the large number of the public comments and their content, ATSDR decided to assemble an expert panel of scientists to critically review a large subset of the public comments and how ATSDR proposes to address them. The Agency also encouraged the expert panelists to comment on any section of the toxicological profile that they thought should be revised.

This expert panel review is an integral part of the overall review process for the Toxicological Profile for PCBs and is expected to lead to a greater understanding of the scientific issues related to PCBs in the environment. ATSDR plans to carefully consider the expert panelists' comments, as summarized in this report, as it finalizes the Toxicological Profile for PCBs.

### **1.2 The Expert Panel**

To organize a comprehensive review, ATSDR identified expert scientists who do not work for the Agency and have demonstrated expertise in the chemical and physical properties of PCBs, human exposure to PCBs, or the health effects associated with PCB exposure, whether in laboratory animals or humans. These scientists included representatives from academia and various federal health and

environmental agencies, and their collective expertise spanned virtually every subject matter in the draft toxicological profile. Therefore, the scientists offered a broad and balanced perspective on the wide range of public comments that ATSDR received. ATSDR distributed copies of the draft toxicological profile, the Agency's proposed disposition of the public comments, and additional relevant information to the scientists roughly 2 weeks prior to the expert panel meeting.

Additionally, several other scientists attended the expert panel review meeting, and they fell into two general categories. First, between 15 and 20 scientists from ATSDR and its profile contractor attended the meeting. These scientists primarily observed the expert panelists' discussions, but offered their own comments and asked the panelists questions periodically throughout the meeting. Second, two observers representing the industry, who ATSDR invited, attended the meeting. The observers mostly listened to the expert panel review, but were given the opportunity to make comments on every topic that was discussed.

Appendix A lists the names and affiliations of the expert panelists, ATSDR scientists, and observers who registered to attend the expert panel review meeting. Note, ATSDR invited representatives of selected special interest groups and stakeholders to attend the meeting.

### **1.3 The Expert Panel Review Meeting**

The 3-day expert panel meeting took place at ATSDR's Division of Toxicology conference room in Atlanta, Georgia, on September 27–29, 1999, and generally followed the agenda shown in Appendix B. Three scientists from ATSDR's Division of Toxicology moderated the expert panel meeting: Dr. Malcolm Williams, Dr. Obaid Faroon (Chemical Manager for the Toxicological Profile for PCBs), and Dr. Chris DeRosa (Director of the Division of Toxicology).

The meeting began with introductory remarks from Dr. Henry Falk, Assistant Administrator of ATSDR, and Dr. DeRosa. Dr. Falk opened the meeting by highlighting the importance of having meaningful and accurate toxicological profiles, not only because the profiles are a critical resource for the Superfund program, but also because they are becoming more widely used in other settings. Specifically, toxicological profiles are now being used as source documents by the World Health Organization, health and regulatory scientists, and researchers and teachers. Given the importance of the Toxicological Profile for PCBs, Dr. Falk urged the expert panelists to actively participate in the meeting's discussions. Following on these remarks, Dr. DeRosa briefly reviewed the steps ATSDR has already taken in reviewing the Toxicological Profile for PCBs (e.g., internal Agency review, external peer review, and release for public comment). He then emphasized that the expert panel review is an integral part of



ATSDR's overall scientific review of this document. After these introductory remarks, the panelists and observers introduced themselves, noting their affiliations and areas of expertise.

For the remainder of the meeting, the panelists engaged in free-flowing discussions on the various topics listed in the agenda (see Appendix B). These discussions addressed relevant public comments, ATSDR's responses to the comments, and any other issues pertaining to the agenda items. As the agenda shows, the expert panel spent most of its time discussing how the toxicological profile described the various health effects associated with exposure to PCBs. These discussions covered non-carcinogenic and carcinogenic effects, as well as the basis ATSDR used for deriving a chronic oral minimal risk level (MRL) for exposure to PCBs. Finally, the expert panelists were encouraged to submit written comments, in case they did not have the opportunity to provide comments during the 3-day meeting.

#### **1.4 Report Organization**

During the meeting, the panelists commented both on general issues that pertain to the entire toxicological profile and specific issues for particular sections in the profile. Section 2 of this report summarizes the general issues raised by the panelists, and Section 3 summarizes the specific issues. Within Section 3, each subsection reviews the panelists' comments on different chapters within the profile (e.g., Section 3.1 summarizes the comments on Chapter 1 of the profile, Section 3.2 summarizes the comments on Chapter 2, and so on). Section 4 of this report lists all references cited in the text. When citing specific passages in the toxicological profile, this report refers to page numbers in the December 1998 release of the draft profile for public comment.

As noted earlier, the appendices to this report include a list of the scientists who registered to attend the expert panel review (Appendix A) and the meeting agenda (Appendix B).



## **2.0 GENERAL COMMENTS ON THE TOXICOLOGICAL PROFILE**

During the 3-day meeting, the expert panelists' discussions primarily focused on specific topics and public comments relevant to the toxicological profile. Section 3 of this report reviews salient features of these specific comments. Some of the panelists' comments, however, were relevant to the entire toxicological profile. These general comments addressed both format issues and content issues, as described below.

### **2.1 Format Issues**

The panelists recommended that ATSDR consider modifying several aspects of the format of the toxicological profile. Most importantly, several panelists and observers thought the profile was very redundant due to the organization of the document: In the current profile, health effects are organized by route of exposure first (inhalation, oral, and dermal), and by endpoint second (e.g., death, systemic effects, reproductive effects, and so on). Noting that the health effects associated with PCBs are believed to be largely, though not exclusively, independent of route of exposure, the panelists almost unanimously recommended that ATSDR organize Chapter 2 of the profile by endpoint first, and by route of exposure second.

The panelists recommended several other changes to the format of the document. First, one panelist recommended the use of "running headers" on every page of Chapter 2, such that readers can easily find the subject matter of every page. Second, another panelist thought Chapter 2 would benefit from the use of sub-headers that clearly distinguish studies on acute, intermediate, and chronic exposures, and that distinguish different types of health effects for a given endpoint. Some panelists thought the use of sub-headers is particularly important for the section on developmental effects (Section 2.2.2.6), which discusses behavioral effects, thyroid effects, and so on. Third, one panelist recommended that every section in Section 2.2 open with one or two sentences explaining the section's contents and including cross-references to other sections, as appropriate. Finally, a panelist suggested that the profile include an index.

### **2.2 Content Issues**

According to the expert panelists, the following issues and general comments apply to the content in various sections of the toxicological profile. The panelists recommended that ATSDR consider revising the relevant sections of the profile accordingly.

- **Synthesis of Information.** Several panelists thought the toxicological profile should be strengthened by including brief sections that synthesize the findings of various toxicological and epidemiological studies presented in Chapter 2. The panelists thought this was especially

important for the Relevance to Public Health section (Section 2.5). According to several panelists, this section currently lists the results of many different toxicological studies on animals and humans, leaving the reader with the burden of drawing conclusions or identifying common themes among them. A few panelists were particularly concerned about the lack of synthesis of information on developmental effects: The panelists thought the profile merely provided a list of studies, without highlighting consistencies and discrepancies between them.

- **Omission of Relevant Studies on PCBs.** Several panelists noted that the current version of the toxicological profile does not include recently published studies on PCBs, as well as some older references. Section 3 of this report identifies specific cases where relevant references were apparently missing or not cited. Responding to this comment, representatives from ATSDR noted that studies published in 1999 and in the last half of 1998 obviously could not be included in the draft profile, since it was published in December, 1998; however, some panelists noted that selected earlier studies were not referenced. The panelists debated whether the profile should include more information on the Yusho and Yu-Cheng poisoning incidents, as Section 3.2.1 of this report describes in greater detail.
- **The Profile's Emphasis on Fish Consumption.** Several panelists thought the toxicological profile overly emphasized, or incorrectly characterized, human exposure to PCBs through consumption of contaminated fish. One panelist explained that this exposure pathway is an important issue for certain populations (e.g., people who consume sport-caught fish from PCB-contaminated waters), but he thought the profile should not overstate this pathway's relevance to the general population.

On a related note, some panelists were concerned that the profile relies too heavily on studies of health effects among fish-eating populations, assuming PCB exposure, and not heavily enough on studies that have identified health effects attributed specifically to PCB exposure. Though they agreed that fish-eating populations are undoubtedly exposed to PCBs, some panelists cautioned that fish-eaters are also exposed to other persistent, bioaccumulative toxicants, thus complicating efforts to attribute observed health effects in epidemiological studies specifically to PCBs. Accordingly, some panelists thought the profile should place a lesser emphasis on the studies of fish consumption, but others thought these studies were an important part of the profile's message.

- **Presentation of Congener-Specific Information.** A recurring topic during the meeting was the fact that the many toxicological and epidemiological studies addressed exposures to various forms of PCBs, including congeners and/or mixtures of congeners. The panelists had differing opinions

on how the profile should address congener-specific information: Some panelists thought it should be presented in separate sections of the profile; others thought including the congener-specific information under the appropriate endpoints would help highlight similarities and differences between exposures to individual congeners, commercial mixtures of PCBs, mixtures of PCBs with other contaminants, and weathered commercial PCB mixtures; and one panelist suspected that including congener-specific effects throughout the profile might make the document difficult to read.

When discussing the availability of congener-specific data, the panelists raised several related issues: One panelist noted that examining associations between total PCB exposure and observed health effects might mask statistically significant findings between exposure to individual PCB congeners and selected health effects. On another issue, one panelist explained that exposure at Superfund sites is primarily to weathered mixtures of PCBs, which might differ considerably from the various commercial mixtures used in selected animal studies. Finally, yet another panelist cautioned ATSDR about relying too heavily on congener-specific information, given the differing sensitivity of various PCB analytical methods.

- **Miscellaneous General Comments.** One panelist encouraged ATSDR to use precise terminology for symptoms (effects that you cannot see, like headaches) and signs (effects that you can see, like rashes). Since symptoms technically are subjective, this panelist thought the profile should not refer to “subjective symptoms,” as it currently does, for example, on page 220.



### **3.0 SPECIFIC COMMENTS ON THE TOXICOLOGICAL PROFILE**

This section summarizes the panelists' review of specific topics in the toxicological profile. Comments are organized by the various chapters in the profile, and comments on health effects are further classified by endpoint. Note, panelists and observers were given the opportunity to comment on every chapter in the draft toxicological profile, but the majority of their comments addressed the health effects outlined in Chapter 2.

#### **3.1 Comments on Chapter 1—Public Health Statement**

Given the number of revisions the panelists recommended to the Public Health Statement, as documented below, and the fact that the Public Health Statement is the most important chapter of the profile to certain audiences, some panelists recommended that ATSDR carefully read through and revise this entire chapter to ensure that it provides a clear and concise statement of the relevant public health issues. Specific examples of the panelists' concerns regarding this chapter follow.

Several panelists highlighted specific passages in the Public Health Statement that were either unclear or inaccurate. For example, one panelist questioned the reasoning behind one of the opening statements in Chapter 1: "Because the health effects of PCBs are difficult to evaluate, most of the information in this document is about seven types of commercially available PCB mixtures" (pages 1 and 2). This panelist suspected that the decision to evaluate seven types of mixtures was not simply due to the complexity of evaluating PCB-related health effects. Further, another panelist questioned the profile's definition of the half-life of PCBs in air ("the time it takes for one-half the PCBs to change into something else," page 3), indicating that this definition does not account for fallout or other relevant removal mechanisms. As a result, the panelists recommended that ATSDR clarify its definition of half-life in the final release of the profile.

Finally, yet another panelist was not convinced that a statement on the toxicity of PCB metabolites was accurate: "Some metabolites of PCBs may have the potential to be as harmful as unchanged PCBs, but there is no conclusive experimental evidence to support this assumption" (pages 5 and 6). The panelists suggested rewording this sentence as: "Some metabolites of PCBs may have the potential to be as harmful as unchanged PCBs; recent experimental evidence demonstrates that metabolites may also cause different kinds of toxicities." This panelist also recommended that ATSDR revise its statement, "If your PCB levels in these fluids are higher than the normal environmental levels, this will show that you have been exposed to high levels of PCBs" (page 10), because prolonged low-level exposure to PCBs might also explain elevated body burdens.

In addition to the specific comments, the panelists discussed the availability and implications of medical tests to characterize PCB levels in blood, body fat, and breast milk. Though the profile clearly states that routine clinical tests are not available, some panelists suggested that ATSDR include more detailed information on this topic, such as whether tests will be commercially available, how people can get tested by physicians and specialists, and how medical professionals should interpret the significance of measured PCB levels. During this discussion, several panelists indicated that the profile does not acknowledge that no treatments are currently available to reduce body burdens of PCBs. One panelist noted that PCB tests are currently available to physicians, but some testing methods have relatively high detection limits and inadequate quality assurance measures.

Noting that exposures to chemicals at waste sites have affected certain communities more so than others, one panelist recommended that the profile, particularly the Public Health Statement, address issues of differential exposures among various ethnic groups. Based on historical data on pesticides, this panelist thought African-Americans might be more likely to store PCBs in their bodies than other sub-populations, but he was not aware of such data on PCBs. To put this comment into perspective, one panelist noted that the African-American women and white women in a study of 912 North Carolinians generally had comparable levels of PCBs, though he added that this data does not reflect exposures at hazardous waste sites (Rogan et al. 1986). At the end of this discussion, ATSDR noted that the profile will address genetic polymorphism with regards to PCB exposure, metabolism, and health effects, if relevant data exist.

General comments on the Public Health Statement included a suggestion that the chapter include a picture indicating the chemical structure of PCBs and a discussion on PCBs in breast milk and nursing. On the latter topic, some panelists questioned whether women with elevated PCB concentrations in breast milk should nurse, but others cautioned against making such statements given the potential benefits of breast feeding. A few panelists wondered if the Public Health Statement should address this topic. Finally, a panelist thought the Public Health Statement should include some information on PCB-related immunological effects, especially considering that ATSDR proposed basing its chronic oral MRL on this endpoint.

### **3.2 Comments on Chapter 2—Health Effects**

The expert panel discussed and debated many technical issues presented in Chapter 2 (“Health Effects”) of the toxicological profile. The following subsections review these discussions, organized by endpoint. The subsections are presented in the order that topics were considered during the expert panel review; this order does not reflect any judgment on which endpoints are most important or most widely debated for PCBs.



### 3.2.1 Developmental Effects

The panelists reviewed public comments the Agency received regarding developmental effects following oral exposure to PCBs. With few exceptions, which are noted below, the panelists generally agreed with ATSDR's proposed approaches for responding to the comments. The observers had no comments on the profile's review of developmental effects. Discussions on developmental effects focused primarily on the following topics:

- **Inclusion of Additional Studies.** In response to a public comment, the panelists listed several relevant studies that are currently not included in the draft toxicological profile. These studies include the Oswego studies (Lonky et al. 1996; Stewart et al. 1999), the Dutch cohort study (Huisman et al. 1995; Koopman-Esseboom et al. 1994, 1996a, 1996b; Lanting et al. 1998a, 1998b, 1998c, 1998d; Patandin et al. 1997, 1998a, 1998b, 1998c, 1998d, 1999a, 1999b; Weisglas-Kuperus 1998), the German cohort study (Winneke et al., 1998), studies published by Dr. Deborah Rice (Rice 1999a, 1999b), and the 2-year follow-up study of a cohort of children in North Carolina (Rogan and Gladen 1991). In addition, the panelists debated the need for providing more detailed analyses of two Asian poisoning incidents—a topic that is elaborated on below.

Some panelists noted that information in the aforementioned studies should have been included in the levels of significant exposure (LSE) tables and could have been relevant to developing an MRL. Overall, several panelists encouraged ATSDR to reconsider the general message of the developmental effects of the toxicological profile (i.e., "The overall evidence suggesting that PCBs may represent a developmental hazard for human health is inconclusive," page 225), given the emerging weight of evidence provided by these additional studies. Moreover, given the range of suggested improvements for the section on developmental effects, some panelists thought future drafts of this section would benefit from additional expert review.

- **Yusho and Yu-Cheng Incidents.** Several panelists recommended that ATSDR consider including more information on the Yusho and Yu-Cheng poisoning incidents from Japan and Taiwan, respectively, in the Toxicological Profile for PCBs. These incidents involved two populations that consumed rice oil contaminated with complex mixtures of chemicals, which included furans, PCBs, and other compounds. Analyses of these incidents are documented in numerous journal articles (e.g., Hsu et al. 1994; Masuda 1994). The panelists offered several insights on the relevance of these studies to the profile.

First, noting that the exposed populations in these incidents consumed mixtures of chemicals, one panelist thought this study should be included in the profile to characterize possible interactive

effects (e.g., synergism and antagonism) of PCBs, furans, and other chemicals. Second, panelists debated the extent to which PCBs, as opposed to furans, accounted for the observed health effects. One panelist indicated that toxic equivalency factor (TEF) calculations have suggested that PCBs accounted for at least 25 percent of the toxicity in the Yusho and Yu-Cheng incidents. For this reason, the panelist thought the toxicological profile should more prominently acknowledge the implications of the Yusho and Yu-Cheng incidents, while noting the uncertainty associated with TEF calculations. Third, the panelists debated whether the exposure concentrations for these incidents had been accurately characterized. One panelist thought the concentrations in the rice oil were extremely well documented. Others agreed, but wondered if heating the rice oil (as the residents of Yusho and Yu-Cheng did when cooking) might have changed the composition of contaminants considerably. As a result, these panelists suspected that levels of the lower-chlorinated PCB congeners might not have been completely characterized. These issues regarding the levels of contamination in the rice oil and potential exposure concentrations were not resolved. Finally, some panelists thought the toxicological profile for PCBs should at least include references to the toxicological profiles on dioxins and furans, which reportedly review the Yusho and Yu-Cheng incidents more thoroughly.

- **Public Comment on the Studies Published by Jacobson.** One of the public comments requested that the toxicological profile provide “a more detailed and balanced summary of the limitations” of the Michigan fisher studies published by Dr. Joseph Jacobson (Jacobson and Jacobson 1996a, 1996b; Jacobson et al. 1984a, 1985). The panelists thought that including results from the Oswego and Dutch studies in the toxicological profile might address the concerns raised in the comment, since these studies replicate the findings of the Jacobson studies under question.

A panelist who is a principal investigator of the Oswego studies then summarized major findings from his research (Lonky et al. 1996; Stewart et al. 1999). He explained how his series of studies overcomes many of the criticisms of Dr. Jacobson’s earlier studies, such as control for confounding variables, quality of sample, and representativeness of analytical data. As a result, this panelist thought inclusion of his studies in the toxicological profile would provide a much more compelling case for links between PCB exposure and neurodevelopmental effects.

- **Public Comment on Paneth’s Criticism of the Jacobson Studies.** One of the public comments suggested that ATSDR’s interpretation of Paneth’s critique of the Michigan fisher studies (see page 125 of the profile) was misleading (Paneth, 1991). ATSDR’s disposition of comments defended its original text by noting that “many other well known researchers,” in addition to Paneth, have criticized the Michigan fisher studies. The panelists discussed this comment and

ATSDR's response at length. One panelist recommended that ATSDR's disposition of comments cite individual scientists and their relevant reviews, rather than simply citing "well known researchers."

Two panelists were surprised at the extent to which the profile stands by Paneth's criticisms of the Michigan fisher study. Noting that Paneth apparently misunderstood the scope of the Michigan fisher study (e.g., by assuming that the Michigan study was a case-control study, which it was not), one panelist thought ATSDR should more carefully review Paneth's criticisms. Agreeing with this sentiment, another panelist thought ATSDR gave an imbalanced account of developmental effects by citing Paneth's criticisms of various studies without citing other reviews that refute these criticisms, especially the "Workshop Report on Developmental Neurotoxic Effects Associated with Exposure to PCBs" (EPA/630/R-92/004). None of the panelists supported Paneth's criticisms of the Michigan fisher study.

- **Recommended Revisions to the Discussion of Neurodevelopmental Effects.** One panelist thought the profile's review of developmental and behavioral effects in animals was very vague and imprecise. As an example, the panelist noted that several passages in this section of the profile discussed how studies observed "a change" or "a behavioral effect," rather than describing the effects and changes in greater detail (e.g., "an impairment" or "an improvement"). This panelist thought ATSDR should include more specific terminology throughout this section for it to be more informative to the reader.
- **The Need for Better Synthesis of Information.** Several panelists were concerned that the toxicological profile, particularly the section on developmental effects, provides little or no synthesis of the information from the many studies presented. Some panelists thought many readers might not be able to identify or understand consistencies and inconsistencies among the myriad toxicological and epidemiological studies. As an example of how the document could better synthesize information, one panelist noted that some animal and human studies have reported similar findings that both humans and animals exposed to PCBs do poorer on tests of memory function. This panelist thought the profile should highlight such parallels between human and animal studies as converging evidence on the link between PCBs and selected health outcomes.

Another panelist thought Section 2.5 (page 224) does not adequately distinguish the implications of transplacental and breast milk exposure. This panelist thought the profile should emphasize that transplacental transfer occurs at the earliest stage of life, when humans are particularly prone

and susceptible to the potential effects of exposure to environmental contaminants, while breast milk exposure occurs slightly later in life and does not appear to be associated with adverse developmental effects.

- **Public Comment on the Findings Reported by Pantaleoni et al (1988).** One public comment suggested that passages on pages 131, 133, and 224 of the profile do not accurately characterize the findings reported by Pantaleoni et al., but the panelists disagreed with the comment and agreed that ATSDR has accurately described this study.
- **Comments on the Mechanisms for Developmental Effects.** One panelist offered three recommendations for improving the profile's discussion on mechanisms for developmental effects. First, this panelist thought Section 2.4.2 implies that neurotoxic effects are linked to exposures to only ortho-substituted PCB congeners, and not to other PCB congeners; the panelist did not think evidence existed proving that non-ortho-substituted congeners do not exhibit neurotoxic effects and recommended that this point be clarified. Second, this panelist thought effects of long-term potentiation might be a more relevant model for evaluating mechanisms of neurotoxicity (as opposed to nerve cell death or reduction in dopamine levels), since these effects appear to follow exposures to doses similar to those encountered in the environment. The panelist noted that some researchers (e.g., Winneke) have examined this mechanism. Third, this panelist recommended that relevant information on mechanisms and *in vitro* studies should be included for perspective in Section 2.2 of the profile, rather than keeping this information only in Section 2.4.

### 3.2.2 Neurological Effects

The panelists reviewed ATSDR's disposition of five public comments regarding neurological effects following both inhalation and oral exposure to PCBs. One observer commented on neurological effects, as noted below.

- **Distinction Between Neurological Effects and Developmental Effects.** A public comment, and several panelists, wondered why certain studies on neurological effects are presented in Section 2.2.2.6 (Developmental Effects) and others are presented in Section 2.2.2.4 (Neurological Effects). In response, the Chemical Manager explained the hierarchy ATSDR follows when classifying effects in toxicological profiles: Any effect observed between conception and maturation is considered a developmental effect, regardless of whether the effect was neurological, systemic, and so on. Though the panelists did not question this approach, several thought the profile should clearly state ATSDR's criterion for classifying neurological effects in two different parts of the document.

- **Public Comment on the Weight of Evidence for Neurological Effects.** Two public comments identified inaccuracies and misleading statements throughout Section 2.2.2.4 and questioned whether sufficient evidence is available linking PCB exposures to neurological effects. A panelist who has conducted her own research on PCB-related neurological effects agreed that this section includes gross inaccuracies and cited as examples misleading statements in the first two sentences of Section 2.2.2.4 (page 117). First, this panelist thought the opening sentence, which indicates that neurotoxic effects have occurred among Native Americans who eat PCB-contaminated fish, should include a reference; this panelist was unaware of any research that had reported such a finding.

Second, this panelist took exception to how the second sentence of this section characterizes her own research (Schantz et al., 1996). The sentence in question implies that her research has found evidence of neurological effects among adults in a fish-eating population and that behavioral outcomes were found to be linked to exposures to ortho-substituted PCBs. However, this panelist explained that the reference cited (i.e., Schantz et al., 1996) simply describes the neurological endpoints that would be assessed and the characteristics of the sample that would be tested in her study. She explained that the actual study is still underway, data analysis is ongoing, and the final results are currently unknown. She thought these and other inaccuracies need to be corrected, because they currently imply that studies have found evidence of neurological effects in adults. Overall, this panelist did not think sufficient evidence existed linking neurological effects in adults with exposure to PCBs, primarily because no research on neurological effects in adults has been conducted.

Other panelists also addressed these public comments. One panelist thought, and others agreed, that some peer-reviewed papers from the Yusho and Yu-Cheng incidents have reported PCB-related neurological effects in adults, including numbness and nerve conduction delays (Chen et al. 1985a; Chia and Chu 1984, 1985). An observer, on the other hand, recommended that ATSDR not include the Asian poisoning incidents under the review of neurological effects, given the uncertainties associated with attributing toxic effects to both the PCBs and furans in the contaminated rice oil. Another panelist recommended, and an observer agreed, that ATSDR review the occupational medicine literature relative to PCBs for more information on potential neurological effects. The observer, however, believed that the occupational medicine literature does not provide evidence of PCB-related neurological effects. Yet another panelist thought the profile should carefully state the overall conclusion for neurological effects: This panelist

encouraged that the profile indicate that not enough evidence is available to determine the links between PCB exposure and neurological effects, if any, rather than imply that no such links exist.

- **Public Comment on Neurological Effects Linked to Inhalation Exposure.** One comment suggested that Section 2.2.1.4 does not accurately portray findings of the three studies on neurological effects following inhalation exposure to PCBs (Fischbein et al., 1979; Emmett et al., 1988a; Smith et al., 1982). According to the disposition of comments, ATSDR plans to revise this section of the profile accordingly. The panelists had no comments on this topic.
- **Public Comment on the Neurotoxicity of Ortho-Substituted Congeners.** One public comment questioned the profile's implications that only ortho-substituted PCB congeners are neurotoxic (see page 117, for example). A panelist proposed that ATSDR address this comment by considering studies on long-term potentiation effects, which reportedly are observed following exposures to both ortho-substituted and coplanar PCBs. No other comments were offered.

### 3.2.3 Children's Susceptibility

The panelists reviewed the four public comments on children's susceptibility to PCBs. An overview of the panelists' views on the public comments, plus some general comments on the Children's Susceptibility section of the profile, follow. The observers had no comments on this topic.

- **Public Comment on the Relevance of Children's Susceptibility for PCBs.** A public comment indicated that the toxicological profile overemphasizes children's susceptibility to PCBs and that the potential health risks to children are no greater than those to adults. Several panelists, however, thought this comment has little substance, for various reasons. First, one panelist noted that children do consume elevated levels of PCBs from breast feeding—a route of exposure that obviously does not affect adults. This panelist also believed that some dietary surveys suggest that children consume more PCBs per body weight than adults. According to another panelist, some recent unpublished data indicate that children who live near selected PCB-contaminated sites have higher PCB tissue concentrations than adults. Given recent studies showing adverse health effects in children associated with low doses of PCBs (see Section 3.7 of this report) and the overwhelming evidence for developmental sensitivity in animal studies, one panelist recommended that ATSDR simply reject the public comment.
- **Public Comment on the Implications of Children's Susceptibility on the MRL.** A public comment suggested that ATSDR not use an uncertainty factor of 10 that accounts for children's susceptibility when developing its chronic oral MRL. (Note, ATSDR's derivation of the MRL in

the draft toxicological profile does not include such an uncertainty factor.) When responding to this comment, the panelists and ATSDR discussed at length the scientific basis for uncertainty factors, ATSDR's approach to, and requirements for, considering uncertainty factors, and the distinction between uncertainty factors and margins of safety. One panelist was concerned that health effects are currently occurring at exposure doses comparable to the proposed MRL. At the end of the discussion, some panelists recommended use of additional uncertainty factors for the purpose of being protective of children, and others did not. The panelists revisited this topic when reviewing the basis for ATSDR's proposed MRL (see Section 3.7 of this report).

- **Public Comment on the Criticisms of the Michigan Fisheater Studies.** A public comment suggested that Section 2.7 of the toxicological profile overstates the value of the Michigan fisheater studies. Consistent with their earlier comments regarding developmental effects (see Section 3.2.1 of this report), the panelists again disagreed with the comment's implication that the findings of the Michigan studies are erroneous.
- **Public Comment on Metabolism of PCBs by Breast-fed Infants.** A public comment questioned whether the profile's reference to studies from 1966 and 1977 (page 239) regarding metabolism of PCBs by infants might be outdated and wondered whether pediatricians still prescribe novobiocin, an antibiotic that reportedly inhibits glucuronyl transferase activity (Gartner and Arias, 1966; Leeder and Kearns, 1977). One panelist suspected that more recent studies are not available from the current scientific literature, but he basically found the comment irrelevant, since he thought breast milk does not contain metabolizable PCBs. Another panelist noted that relatively small amounts of metabolizable PCBs are occasionally detected in breast milk, but in small proportions; he added that these infrequent detections presumably occur in individuals recently exposed to PCBs. This reviewer stressed that the epidemiological significance of these infrequent detections has not been established.
- **General Comments on Children's Susceptibility.** After reviewing the public comments on children's susceptibility to PCBs, some panelists offered general remarks on this topic: Two panelists thought the children's susceptibility section should acknowledge the sensitivity of the thyroid system (see Section 3.2.4 of this report), though neither cited published studies reporting a link between PCB exposure and thyroid effects in children. Another panelist indicated that the recent studies by Deborah Rice should also be included in the children's susceptibility section (Rice, 1999a; 1999b).

#### 3.2.4 Endocrine Effects

The panelists reviewed ATSDR's disposition of every comment the Agency classified as specifically addressing endocrine effects of PCB exposure. The observers had limited comments on these discussions.

- **Inclusion of Additional Studies.** When reviewing the public comments on endocrine effects, the panelists listed several studies that ATSDR should consider incorporating in the toxicological profile. One panelist thought the profile should include more data from human studies, specifically the Yusho incident and the Dutch studies (Koopman-Esseboom et al. 1994; Nagayama et al. 1997; Weisglas-Kuperus 1998), to provide a more complete account of endocrine effects. This panelist thought data from the Yusho incident provides insight on potential interactive effects between PCBs and other compounds. Another panelist thought the profile should more prominently acknowledge *in vitro* studies of PCB congener-specific activities, human cell lines, and so on. Yet another panelist recommended, and an observer agreed, that the profile should address Arnold's studies of endometriosis (Arnold, 1996) and Helzlsouer's studies of breast cancer (Helzlsouer et al., 1999).
- **Organization, Prioritization, and Synthesis of Endocrine Effects in the Profile.** In response to a public comment regarding the profile's redundant discussions of endocrine effects, panelists noted that ATSDR could address this comment by revising the profile's format, as described in detail in Section 2.1 of this report. In addition, one panelist felt the profile placed too much emphasis on studies on endometriosis and breast cancer and not enough emphasis on thyroid effects, for which extensive animal studies and limited human studies are reportedly available. Given the large volume and complexity of information on endocrine effects, two panelists thought the toxicological profile should include a brief integration and synthesis of the many studies reviewed.
- **Public Comment on the Xenoestrogen/Breast Cancer Theory.** A public comment recommended that the discussion of xenoestrogen/breast cancer theory (pages 233 and 234) be deleted from the toxicological profile. The panelists debated at length the utility of including various theories linking PCBs to breast cancer, as described below. Overall, one panelist did not think the toxicological profile should include such theoretical discussions given that scientists have little understanding of the endocrine causal pathway for breast cancer. Other panelists thought the discussions were relevant to the toxicological profile, but recommended that ATSDR move them into the profile's sections on cancer. (In fact, the panelists continued to discuss this topic in their review of the sections on cancer; see Section 3.2.5, below, for additional comments.)



The panelists provided several different perspectives on the theory of PCBs and breast cancer. One point of agreement was that the draft toxicological profile presents a very selective review of the current literature on breast cancer and environmental contaminants; one panelist noted that the profile omits a recent study that found no association between PCB serum concentrations and breast cancer (Helzlsouer et al., 1999).

Though the panelists also generally agreed that the relevant epidemiological studies currently do not support a link between PCB exposure and breast cancer, they offered different reasons for why no such link is apparent. For example, one panelist noted that the causal pathway for breast cancer might begin very early in life, in which case, studies that examine PCB levels in adult subjects would naturally not capture the exposures that might be of greatest concern. Alternatively, other panelists noted that the epidemiological studies generally have inadequate characterization of serum levels of PCBs: Emphasizing that some PCB congeners are estrogenic and others are anti-estrogenic, one panelist thought studies that reported serum levels of total PCBs are inadequate, since this metric does not characterize the estrogenicity of the exposure concentrations; another panelist indicated that some epidemiological studies collected too few serum samples (and not at relevant times) to provide a meaningful data analysis; and yet another panelist noted that many of the epidemiological studies did not consider serum levels of dioxins and furans, which might be confounding factors in establishing links between PCBs and breast cancer. The expert panelists' varying comments and criticisms suggested that the available human studies offer little insight into the exact role PCBs have, if any, in causing breast cancer.

- **Public Comment on the Mendola Study (1997).** A public comment noted that the shortened menstrual cycles observed in women who consumed fish, as documented in the Mendola study, cannot be attributed to PCB exposure, since the fish likely contained other persistent toxins. One panelist agreed with the comment, but thought research like the Mendola study is still germane to the toxicological profile, even though the findings might indicate results of interactive effects of many contaminants. This panelist recommended that ATSDR retain such studies in the toxicological profile and bring the associated issue of interactive effects to the forefront.
- **Public Comment on the Mendola (1997) and Gerhard (1998) Studies.** A public comment suggested that the studies published by Mendola and Gerhard should be deleted from the toxicological profile because they do not provide direct evidence of PCB-related endocrine effects. Disagreeing with the comment, one panelist recommended that the studies be retained in the profile with appropriate caveats noting their limitations; this panelist also suggested reinforcing

the findings of these studies with relevant animal studies, if available. No other panelists addressed this public comment.

- **Comments on Thyroid Effects.** Two panelists thought the toxicological profile should have included more information on thyroid effects. These two panelists noted that current research has not reported consistent thyroid effects associated with exposures to PCBs: Different effects are observed in different human cohorts, thus underscoring the complexity of understanding the mechanisms of thyroid effects. Though these panelists acknowledged that inconclusive data are available for humans, they recommended that the profile review the available information. One panelist recommended that ATSDR refer to a recent issue of Environmental Health Perspectives for a review of relevant epidemiological studies that might provide additional information on thyroid effects (Brouwer et al. 1999).
- **Inclusion of Discussions on Diabetes and the Pancreas as a Target Organ.** Though he acknowledged that only limited information is available on these topics, one panelist was concerned that the toxicological profile does not discuss possible links between PCB exposure and diabetes, nor does it mention the pancreas as a target organ. This panelist noted that PCBs have been found to cause beta cells in the pancreas to release insulin. He then recommended that the profile at least mention potential links between PCBs and diabetes as an emerging issue, especially given the growing evidence of links between dioxin exposure and diabetes compiled by the National Institute of Health Sciences.
- **Additional Comments on the Endocrine System.** Some panelists thought the profile should review studies that have characterized PCB concentrations in follicular fluids, which could have implications for various target organs and effects. Others thought the profile erroneously classifies all coplanar PCBs as anti-estrogens (see page 234); these panelists indicated that some coplanar PCBs (e.g., possibly PCB #77 and #126) and their metabolites are actually estrogenic.

### 3.2.5 Cancer

The panelists discussed at length the public comments regarding how the toxicological profile documents PCB-related cancer effects, during which the observers offered a few comments. An overview of the panelists' discussion follows.

- **Public Comment on the Carcinogenicity of PCBs.** A public comment took exception with a passage in the toxicological profile that claimed "most of the epidemiological studies have been inconclusive or have not shown an association between PCBs and cancer" (see page 138). In their

discussions, the panelists unanimously agreed that ATSDR should, *throughout the toxicological profile and disposition of comments*, simply refer to the carcinogenicity classifications made by the U.S. Environmental Protection Agency (EPA), the International Agency for Research on Cancer (IARC), and the National Toxicology Program (NTP). The panelists encouraged that ATSDR review these classifications carefully and even incorporate EPA's, IARC's, and NTP's specific terminology regarding cancer effects in humans and animals.

During this discussion, a panelist indicated EPA's current position on the carcinogenicity of PCBs: PCBs are probable human carcinogens, based on suggestive but inadequate human studies, and animal studies that provide sufficient evidence. This panelist was surprised that the toxicological profile currently implies that there is no association between PCBs and cancer, rather than paralleling EPA's position.

Citing a different quote in the profile ("The weight of evidence does not support a causal association for PCBs and human cancer at this time," page 227), one panelist suggested that ATSDR use precise terminology and clearly differentiate discussions of causation from those of association when commenting on the carcinogenicity of PCBs. Another panelist indicated that the Public Health Statement (Chapter 1) does not clearly communicate the current state of knowledge regarding PCBs and cancer. Yet another panelist was concerned about the overview of PCBs and cancer in the section on Relevance to Public Health (Section 2.5). These panelists thought, and others agreed, that ATSDR needs to carefully revise the profile to avoid presenting a confusing, inconsistent account of carcinogenicity.

- **Public Comment Providing Evidence that PCBs Are Not Carcinogens.** One public comment suggested that the toxicological profile should conclude that PCBs are not human carcinogens, based partly on the fact that similar cancer endpoints have not been reported across the many different epidemiological studies. The panelists generally disagreed with this comment, for two reasons. First, the panelists noted that IARC's carcinogenicity classification clearly contradicts the comment's assertion.

Second, a couple of the panelists explained that the observation of common cancers across studies is not a necessary and sufficient condition for establishing a contaminant's carcinogenicity. In fact, these panelists noted that the absence of consistent cancer outcomes might simply reflect the small cohort sizes in certain studies, the extremely low incidence of certain cancers, or latency effects. Further, noting that animal studies have reported gender differences in cancer effects, one panelist hypothesized that the varying demographics in the cohort studies might account for part

of the apparent inconsistency in cancer outcomes. Finally, one panelist was not surprised about the variable cancer outcomes, given the fact that the occupational studies considered (1) notably different plant settings, (2) employees with widely varying contacts with PCBs, and (3) exposures to different Aroclor mixtures and other contaminants. In short, the panelists did not agree with the arguments provided in the public comment.

- **Inadequate Review of Occupational Epidemiological Studies.** After citing several instances where the toxicological profile made uninformed criticisms of his epidemiological studies, one panelist recommended that ATSDR carefully review all of the profile's discussions on occupational epidemiological studies before releasing the final draft. In general, this panelist was particularly concerned that the profile characterized what he thought were strengths in his study as either weaknesses or limitations (Sinks et al., 1992). More specifically, he thought the profile unfairly criticizes the selection criteria used in his epidemiological study (see pages 39 and 40), and he defended the criteria as a strength, rather than a limitation. This panelist noted that the criteria (e.g., including all plant workers in the study, regardless of their duration of employment) were entirely appropriate for investigating potential dose-response patterns, which would not have been possible if other selection criteria were adopted.

Expanding on these concerns, another panelist identified cases where the profile unfairly criticized "limitations" of Brown's epidemiological studies (page 36) (Brown 1987; Brown and Jones 1981). This panelist did not see a flaw in "combining two plants from different geographical regions," especially because the Brown study reported results for both the combined populations and for the individual plants. This panelist also disagreed with the profile's statement that "... the appropriateness of grouping liver, biliary, and gall bladder cancers is questionable," partly because International Classification of Disease (ICD) codes, especially ICD codes for subjects who died more than 30 years ago, might actually support grouping these cancers. The panelist recommended that ATSDR verify whether splitting the cancers would have been defensible before citing this approach as a limitation.

In addition to the previous concerns, some panelists suggested that ATSDR's review of occupational studies comment more specifically on the differences in exposures from one plant to the next. A panelist explained that exposures at the Bloomington plant (a facility considered in one of the studies) were likely considerably different from the exposures at General Electric's plants, due to the plants' differing building configurations, industrial processes, and so on. Echoing this concern, another panelist noted that the plants she has studied use widely varying

amounts of chlorinated solvents and other chemicals that should be considered when interpreting results from these types of studies.

On another note, two panelists cautioned ATSDR about classifying occupational studies by route of exposure, since employees at many plants were exposed to PCBs through some combination of inhalation, oral, and dermal exposures, and the dominant route of exposure could have varied from subject to subject. One of these panelists noted that some of the epidemiological studies currently classified under oral exposure might actually be better classified under inhalation exposure. Both panelists thought the profile should at least acknowledge that most subjects in these studies had multiple exposure routes.

By the end of the meeting, several panelists recommended that the final toxicological profile address cancer retrospective cohort mortality studies more thoughtfully and that the revised profile portray the strengths and limitations of these studies more accurately.

- **The Need for a Comparative Overview of Occupational Cohort Studies.** Some panelists strongly recommended that the profile include a table that compares and contrasts key features of the many occupational cohort studies published on PCBs. The panelists noted that such a table should at least clearly indicate exactly what populations were considered in the cohort studies (some different studies actually considered the same cohorts), the location(s) of the cohorts, the availability of dose information, the type of study (prospective versus retrospective), and possibly a brief summary of findings.

The panelists thought such an addition was necessary because even researchers familiar with the literature can get easily confused when trying to make sense of the occupational studies. As an example, one panelist noted that David Brown has published more than one paper that has reported elevated liver and rectal cancers among women who were highly exposed to PCBs (Brown 1987; Brown and Jones 1981), but these papers reportedly document effects observed among a single cohort and not three separate cohorts. The panelists worried that an observer unfamiliar with this literature might interpret the results of these three papers as a consistent finding among separate studies, when, in fact, the papers present a single finding that has been observed in one cohort. The panelists thought the profile should not be ambiguous in this regard.

- **Organization of the Discussions on Cancer.** Noting that he had difficulties quickly identifying the profile's review of PCBs and brain cancer, one panelist recommended that the profile have just one section in Chapter 2 on cancer, with separate sub-sections that address the different types of

cancers. Further, some panelists thought the profile should adopt a more systematic approach for presenting the studies relevant to cancer, possibly by presenting occupational studies first, followed by non-occupational studies, studies evaluating exposures from fish consumption, case-control studies, and animal studies.

- **Lack of Emphasis on Gender Differences.** During their discussions, the panelists identified several instances where gender differences were apparent, but not documented in the profile. For instance, some of the human studies have found notable gender differences, as have selected animal studies (Mayes et al., 1998). As a result, some panelists thought discussion of gender differences should not be limited to the LSE tables, but should also be discussed in the text on cancer effects, and possibly in the Relevance to Public Health or Public Health Statement sections.
- **Public Comment on the Implications of the Most Recent Kimbrough Study.** Citing quotes from a press release that reportedly overstated the findings of the recent Kimbrough cancer study (Kimbrough et al., 1999), a public comment suggested that ATSDR carefully review this study in the final profile. When discussing this comment, copies of a recent letter to the editor criticizing the Kimbrough study (prepared by ATSDR scientists) were distributed to the panelists (Bove et al., 1999). Representatives from ATSDR gave an overview of their findings, after which panelists commented on the Kimbrough study. One panelist noted that some of the limitations identified in ATSDR's review are simply inherent limitations in cohort mortality studies, but this panelist did question some of the data interpretations cited in the Kimbrough study. As an example, this panelist thought the study's data are suggestive of female intestinal cancer—a conclusion that is apparently not reached in the paper.
- **Public Comment on Links Between PCBs and Melanoma.** A public comment indicated that the profile overstates the association between PCBs and melanoma that was reported by Loomis et al (1997). The panelists disagreed with this comment, noting that Loomis' analysis of dose-response was an accurate depiction of the cancer outcomes, contrary to the arguments presented in the comment. Moreover, some panelists noted that consistent findings from another study (i.e., Sinks et al., 1992) provide compelling evidence for the association, despite the known genetic and behavioral risks of melanoma.
- **Public Comment on the Profile's Characterization of Breast Cancer Studies.** A public comment criticized the profile for providing inaccurate and incomplete information on the association between PCBs and breast cancer in humans. When reviewing ATSDR's proposed

disposition of this comment, the panelists revisited many of the topics they discussed during their earlier review of endocrine effects (see Section 3.2.4 of this report).

In general, the panelists agreed on some aspects of the profile's review of breast cancer, but disagreed on others. The main point of agreement was that the profile should discuss breast cancer primarily in the "Cancer" sections and not in the "Endocrine Effects" sections. Another point of agreement was that the profile does not provide a balanced review of the current scientific literature, but the panelists had differing recommendations for how ATSDR should address this. Some panelists thought the profile should include a more thorough review of the various studies on breast cancer, reflecting the differing quality of these studies. Several panelists, on the other hand, thought including additional information was unnecessary, suspecting that a thorough review of the literature on breast cancer and PCBs would take too much room in the profile on a topic that is still widely debated.

The main point of contention was whether the toxicological profile should discuss the xenoestrogen/breast cancer theory in the first place. Consistent with their earlier debates, some panelists thought the theory should be omitted from the profile, but others disagreed and thought the profile should briefly mention the theory, along with its uncertainties.

As general comments on PCBs and breast cancer, one panelist recommended that ATSDR integrate summary statements from Hunter's recent review article on breast cancer (Hunter et al. 1997). Another panelist thought the profile should indicate that some genetically vulnerable populations might be more susceptible to carcinogenic effects, which might explain some of the variable results from the epidemiological studies. Other panelists questioned whether the Public Health Statement (page 7) should claim that PCBs "may play an import role in causing breast cancer," given the debate that continues to surround this hypothesis. Finally, one panelist recommended that the profile should note that pre-menopausal and post-menopausal breast cancers might have different etiologies.

As noted earlier, additional comments regarding the profile's handling of breast cancer can be found in Section 3.2.4, above.

- **Comments on PCBs and Non-Hodgkin's Lymphoma.** A public comment thought the profile grossly overstated the findings of the Hardell study on the links between PCBs and non-Hodgkin's lymphoma (Hardell et al., 1996). Two panelists agreed with this comment. Noting that the Hardell study did not directly examine immune markers or any other immune effects, one panelist

thought the profile should not state that this study's “. . . data suggest that the immunosuppressive effects of PCBs may relate to the etiology of non-Hodgkin's lymphoma” (page 139). This panelist instead thought the profile should simply state the main finding of the Hardell study—elevated PCB levels were found to be associated with some cases of non-Hodgkin's lymphoma. The other panelist did not think the profile should report hypothetical mechanisms, especially when little evidence of the mechanisms exist.

The panelists discussed several general issues related to the profile's discussion on non-Hodgkin's lymphoma. First, noting that immunosuppression accounts for a very small portion of non-Hodgkin's lymphoma cases, one panelist emphasized that the absence of evidence linking PCBs to immunosuppression does not necessarily contradict apparent associations between PCBs and non-Hodgkin's lymphoma. Second, though the mechanisms of action might not be known, two panelists thought the profile should underscore the consistent findings of the Hardell study and selected occupational studies (e.g., Betrazzi et al., 1987). One panelist added that the absence of consistent evidence across every occupational study might simply result from the rarity of non-Hodgkin's lymphoma, and not from a lack of association between PCBs and this cancer. Third, the panelists suggested additions to the profile's section on mechanisms of PCBs and non-Hodgkin's lymphoma: One panelist indicated that this mechanism is clearly not Ah receptor mediated; another panelist thought the profile should acknowledge other potential mechanisms (e.g., immunosuppression and reactive oxygen species) for all types of cancers, but some panelists cautioned about including too many hypotheses and theories on cancer mechanisms in the profile.

- **Public Comment on the Rothman Study (1997).** A public comment recommended that the profile note that Rothman's 1997 research on non-Hodgkin's lymphoma was conducted primarily to generate hypotheses and that further research is required to confirm its theories. A panelist clarified that the Rothman study was not designed to generate hypotheses; rather, the study's original design was reportedly to examine associations between cancer outcomes and DDT, but the study happened to generate hypotheses by virtue of its findings specific to PCBs. No other panelists addressed this comment.
- **Public Comment on Sensitivity of Younger Animals to Carcinogenic Effects of PCBs.** A public comment indicated that experimental studies do not suggest that younger animals have greater sensitivity to carcinogenic effects of PCBs. Two panelists disagreed with this comment, however, noting that Dr. Lucy Anderson has published several studies documenting differential sensitivity of immature animals to PCB-related carcinogenic effects (Anderson et al. 1983, 1986, 1993). Further, another panelist noted that studies by Rao and Banerji have characterized PCB-



related carcinogenic effects in 5-week old rats, though these studies did not compare the sensitivity of the immature rats to adult rats (Rao and Banerji 1993).

- **Public Comment on the Bahn et al. Study (Bahn et al. 1976, 1977).** Noting that Bahn's study is in fact a letter to the editor that reports preliminary data, a Submitter suggested that the profile place a lesser emphasis on its results. One panelist thought this particular letter to the editor was an important contribution to the literature, even though Bahn's study results were never published. No other panelists commented on this study.
- **MRLs and Cancer Endpoints.** One panelist wondered if ATSDR will derive an MRL or some other advisory limit that reflects carcinogenic endpoints. Other panelists and ATSDR scientists explained that the MRLs, by definition, are based strictly on non-carcinogenic effects and that ATSDR, as per policy, does not derive advisory limits for cancer effects. Rather, the Agency simply defers to EPA's cancer slope factors for such limits, if appropriate.
- **General Comments on PCBs and Cancer.** When reviewing the profile's treatment of PCBs and cancer, some panelists made general comments that do not fit under the categories described above. Examples of these comments follow: (1) One panelist thought the toxicological profile's summary of Rothman's paper overlooked a notable finding—a potential interaction between cancerous effects and the Epstein-Barr virus. (2) One panelist noted that IARC's document on the carcinogenicity of dioxin reviews studies of cancer among the Yusho and Yu-Cheng populations that might be relevant for the profile on PCBs (Hsu et al. 1985; Kuratsune et al. 1987). (3) One panelist thought the discussion of breast cancer on pages 138 and 139 was unclear, because it did not clearly distinguish the study of fisheaters from the study of blood donors. (4) One panelist indicated that the review of the Mayes animal study should note that dibenzofurans were largely removed from the Aroclor 1254 mixtures that were administered to the rodents, thus strengthening the toxicological implications of the study. (5) One panelist recommended that the profile address cancer slope factors in the section on Relevance to Public Health (Section 2.5), given that these factors have implications to dermal and inhalation routes of exposure. (6) On the topic of PCBs and brain cancer, one panelist thought the profile should consider studies published by Health Canada, Loomis, and Greg Steele (Loomis et al. 1997; the reviewers did not provide references for the studies reportedly conducted by Health Canada and Greg Steele).

### 3.2.6 Reproductive Effects

The panelists stepped through the three public comments regarding reproductive effects. They had no comments on ATSDR's proposed disposition of two comments, but they did discuss the proposed

disposition of the third. An overview of this discussion, plus general comments on PCB-related reproductive effects, follow:

- **Public Comment on the Presentation of Endometriosis Studies.** A public comment took exception to how the profile presented information on PCBs and endometriosis, particularly the profile's suggestion that "... endometriosis is known to occur following exposure to dioxin and some dioxin-like chemicals" (page 122). One panelist thought the profile should include a summary of studies that link dioxin to endometriosis, so long as the profile clearly acknowledges that links between PCBs and endometriosis have not been identified. However, noting that the mechanisms of action of dioxins and coplanar PCBs are similar, this panelist indicated that the lack of information on PCBs and endometriosis does not necessarily imply that the two are completely unrelated.

When discussing this topic, one panelist cited results from Arnold's study on endometriosis in rhesus monkeys: The study reportedly found no correlation between PCB exposure and the incidence of endometriosis, but the study found that monkeys who were fed Aroclor 1254 had longer average menses duration and a shorter average menstrual cycle length than the untreated monkeys (Arnold et al., 1996). Noting that the group of monkeys considered in this study was relatively old, one panelist suggested that a similar study of a younger group of monkeys might generate different results. No other panelists commented on the potential links between PCBs and endometriosis.

- **General Comments on Reproductive Issues.** One panelist thought the profile should have commented more thoroughly on the findings of the Buffalo fisheater study that are relevant to reproductive effects, such as the observed late fetal loss, changes in menstrual cycles, and time-to-pregnancy effects. Noting that some of these findings are currently classified under developmental effects (Section 2.2.2.6), this panelist recommended that the profile clearly state how ATSDR distinguishes research on developmental from research on reproductive effects. Another panelist recommended that the profile document Barsotti's findings regarding reduced reproductive performance in rhesus monkeys up to 5 years following the cessation of dosage of Aroclor 1248 (Barsotti et al., 1976).

### 3.2.7 Toxicokinetics

Most of the panelists did not comment on Section 2.3 of the profile. As an exception, one panelist recommended that ATSDR review its statements on distribution of PCBs to reflect the most recent information available, particularly congener-specific data. This panelist thought the profile had confusing

statements on serum-adipose partitioning (page 160) and should have offered more detail on distribution of PCBs following oral exposure. He thought the profile's treatment of metabolism was adequate.

### **3.2.8 Mechanisms of Action**

When reviewing information on the toxicological endpoints, the panelists offered two general comments on Section 2.4 that are not listed in the previous subsections. First, one panelist recommended that the section on mechanisms of toxicity acknowledge the research by Isaac Pessah on the ryanodine receptor (Pessah 1997; Wong and Pessah 1996, 1997). This panelist believed Pessah's work has noteworthy implications both because it points to a receptor-mediated mechanism for the non-dioxin-like PCB congeners and because the structure-activity data for this receptor correlate with the structure-activities for selected neurotoxic effects. Second, two panelists strongly disagreed with the statement in the profile, "Most of the non-neural toxic and biochemical effects of PCBs occur via a signal transduction pathway involving the Ah receptor" (page 197). They believed that most of these effects occur via pathways that do not involve the Ah receptor and suggested some of these pathways be discussed in the profile.

### **3.2.9 Reducing Peak Absorption Following Exposure**

One panelist recommended, and another agreed, that ATSDR delete or thoroughly revise Section 2.11.1 (Reducing Peak Absorption Following Exposure) because he was unaware of any method, except possibly for lactation, that effectively reduces PCB body burdens in exposed individuals. Another panelist agreed that medical intervention cannot reduce PCB body burdens, but he added that physicians can offer recommendations for minimizing the toxic effects of exposures.

## **3.3 Comments on Chapter 3—Chemical and Physical Information**

The expert panel reviewed ATSDR's proposed disposition of the two public comments relevant to Chapter 3 and offered general comments on the chapter. A summary of the panelists' discussions follows:

- **Public Comment on "Heavy 1254."** A public comment recommended that Chapter 3 include information on "heavy 1254"—a PCB congener mixture similar to Aroclor 1254, but containing higher amounts of dioxin toxic equivalents. One panelist agreed with the comment, particularly because the congener profile for any mixture affects the results and interpretations of human and animal studies. This panelist recommended that the profile indicate the relative toxicity of "heavy 1254," to the extent that such information is available.

- **Public Comment on Revising Table 3-5.** A public comment recommended that ATSDR update Table 3-5 in the profile with more recent information on the congener composition of various Aroclors. The panelist who provided the updated information noted that the data were originally compiled by George Frame, and recommended that ATSDR cite his effort if the Agency uses the revised table in the final profile (Hansen 1999).
- **General Comments on Chapter 3.** The panelists offered several general comments on the profile's presentation of chemical and physical properties of PCBs. First, two panelists thought Chapter 3 should include text that describes, even if generally, how the various chemical and physical properties of PCBs affect environmental distribution and the potential for human exposure. These panelists also recommended that the profile indicate how PCB properties are, to a certain extent, dependent on the number of chlorine atoms in a given congener (e.g., lower-chlorinated PCBs tend to be more water soluble and volatile than the higher-chlorinated PCBs), though they acknowledged that such information could also be logically presented in other chapters of the profile.

An observer indicated that the profile incorrectly identifies the reasons why PCBs were originally used in industry (page 274). This observer noted that fire resistance, rather than chemical inertness, was the primary factor for selecting PCBs for various applications. Consequently, this observer took exception to the profile's characterization of PCBs as "combustible liquids" (also on page 274). ATSDR's profile contractor suspected that this characterization was taken from a Department of Transportation designation of PCB properties, but no panelists or observers could confirm this explanation.

Based on an observer comment, one panelist recommended that the profile provide more detailed information on the chemicals that can be formed upon combustion of PCBs. The observer acknowledged that data suggest that PCBs form furans upon combustion, as the profile indicates, but he did not think sufficient data were available to confirm that PCBs form dioxins. This observer noted that model compound studies have suggested that chlorinated benzenes, which are often found in PCB mixtures, form dioxins upon combustion, but he was unaware of any similar studies suggesting that PCBs form dioxins. Questioning this position, a panelist thought studies of the Yusho incident reported that trace amounts of dioxins were formed upon heating PCB mixtures, but the observers indicated that most of the data suggested otherwise and that only very limited data of questionable quality indicated that PCBs might form dioxins. Overall, the observers and some panelists recommended that ATSDR review its discussion of combustion by-products accordingly (page 274).

Finally, after discussing the history of how PCBs have been used in industry, one panelist recommended that the profile mention the different chemicals, such as chlorobenzenes, that are commonly found in PCBs. This suggestion followed an observer comment on past use of Askarels—a generic grouping of non-combustible electrical fluids that contained PCBs and often, though not always, contained chlorobenzenes. Also relevant to this discussion was the observation that many companies altered the composition of PCB mixtures that were originally prepared by manufacturers.

### 3.4 Comments on Chapter 4—Production, Import/Export, Use, and Disposal

The panelists reviewed the nine public comments ATSDR received on topics in Chapter 4 and the Agency's proposed disposition of these comments. With one exception, the panelists and observers had no additional comments on these topics. Two panelists, however, agreed with the public comment suggesting that ATSDR should consider deleting the entire last paragraph in Chapter 4 (pages 303 and 304), which addresses remedial options for PCB-contaminated sites. The Submitter and the two panelists were concerned that, in this paragraph, ATSDR was “identifying preferred remedial alternatives”—an issue that EPA typically addresses. One panelist suggested that ATSDR merely present the various remedial options without commenting on which options are preferred.

An ATSDR scientist provided one additional comment on Chapter 4, suggesting that ATSDR reconsider including discussions on specific clean-up levels for PCBs in soils (page 302), since some readers might infer that the listed levels should apply to all PCB-contaminated sites. If ATSDR retains the information on soil clean-up levels, one panelist recommended that the profile indicate the soil depth over which these levels apply.

### 3.5 Comments on Chapter 5—Potential for Human Exposure

The expert panel and observers discussed selected public comments ATSDR received on Chapter 5 of the profile. A summary of this discussion follows:

- **Clarification of Exposures Due to Fish Consumption.** One panelist strongly recommended that ATSDR reconsider the profile's summary statements about how the general population is exposed to PCBs. This panelist emphasized an important distinction that the profile should make: Consumption of fish caught in PCB-contaminated waters leads to notably different exposures than consumption of fish purchased in stores. Moreover, this panelist added that the general population primarily consumes tuna, shrimp, catfish, and salmon, all of which reportedly have extremely low PCB levels or no measurable PCBs. Another panelist agreed with this comment.

- **Public Comment on the Reported Serum Levels of PCBs.** A Submitter recommended that ATSDR provide additional context for the serum levels of PCBs (4–8 ppb) reported in the toxicological profile. Some panelists strongly agreed with this sentiment. One suspected that the reported serum levels are based on relatively old data and should be updated with recent figures, if available. After emphasizing that the reported serum levels can have great implications on current public health studies, this panelist recommended that ATSDR carefully consider this public comment and properly caveat the estimated serum levels as necessary. Further, an observer thought the profile should indicate that PCB serum levels generally increase with age. Finally, two panelists suggested that Health Canada might have more recent data for commenting on serum levels of PCBs.
- **Public Comment on the Presentation of Dated Information.** Noting that the profile currently cites some dated exposure concentrations, one Submitter recommended that the document clearly differentiate typical exposure concentrations observed in the past from those observed today. Agreeing with this comment, some panelists noted that much of the exposure concentration data in Chapter 5 is dated. For instance, one panelist indicated that the U.S. Food and Drug Administration (FDA) has recently published information on dietary levels of PCBs that the profile does not cite (a citation for this study was not provided). Reviewing trends in these data, this panelist indicated that current quarterly “market basket” studies now rarely show PCBs at quantitative levels (50 ppb). He added that these current PCB levels are considerably lower than levels that were observed during the 1970s—a trend that several panelists thought the profile should mention. Some panelists wondered whether the average daily intake, when normalized to body weight, suggested by the market basket studies currently exceeds ATSDR’s proposed MRL. This issue was not resolved during the meeting.
- **Public Comment on Current Occupational Exposures to PCBs.** One Submitter thought the profile included an inaccurate account of current occupational exposures to PCBs (“... occupational exposures to PCBs remains several orders of magnitude higher than general population exposure,” page 308). Agreeing with this comment, one panelist noted that elevated PCB body burdens in individuals with occupational exposures might primarily reflect past exposures, and provide little insight into current exposure levels. Based on this and other arguments, some panelists recommended (and an observer agreed) that Chapter 5 better reflect how PCB exposures have changed in occupational settings over the years and specifically identify the occupations that likely have the greatest potential for exposure to PCBs today.

- **Public Comment on Comparability of Various Human Monitoring Findings.** One Submitter suggested that the toxicological profile summarize the significance of the different sampling media (e.g., blood serum, breast milk, and adipose tissue). One panelist indicated that ATSDR could respond to this comment by providing general guidelines for estimating PCB levels in one medium from reported PCB levels in another medium. Other panelists cautioned, however, that such simple partitioning guidelines would likely not apply to all PCB congeners and that congener-specific partitioning has not been extensively documented in the scientific literature.
- **Public Comment on PCB Exposures via Contaminated Drinking Water.** A Submitter took exception to statements in the profile which imply that ingesting contaminated drinking water might be a relevant source of exposure to PCBs (“The general population may be exposed to PCBs by inhaling contaminated air and ingesting contaminated water and food,” page 307). Noting that PCBs are extremely hydrophobic compounds, one panelist agreed with the public comment, even for historical exposures. Another panelist, on the other hand, did not think such statements should be removed from the profile entirely, since “raw water” with high amounts of suspended solids could be a viable exposure pathway for PCBs and since PCBs in water are the major source of contamination to fish. Accordingly, this panelist encouraged that ATSDR acknowledge (rather than ignore) the various potential exposure pathways for PCBs, and put them into proper perspective.
- **Public Comment on Atmospheric Removal Processes.** A public comment questioned whether photolysis is the dominant removal pathway for airborne PCBs, as the profile currently suggests (page 306). One panelist thought precipitation, not photolysis, is the dominant removal pathway.
- **General Comments on Chapter 5.** When addressing the public comments, the panelists offered the following general insights on the technical content of Chapter 5. First, one panelist thought the profile should clearly indicate that the PCB congener profile in most inhalation exposures considerably differs from that in oral exposures. This panelist also thought the profile’s discussion of indoor air exposures places too great an emphasis on PCBs in occupational settings, especially considering that PCBs are now almost never used in industry. Second, one panelist noted that the profile currently uses inconsistent terminology when referring to FDA’s tolerance on PCBs in fish. He explained that this tolerance is a regulatory standard (not a guidance) and is based on PCBs in edible tissue (not a lipid-adjusted value). Another panelist, in response to a public comment, recommended that the profile include a reference for its information on PCB degradation in contaminated sewage sludge (page 305). Yet another panelist, when responding to a different

public comment, suggested that ATSDR consider data from the National Human Exposure Assessment Survey (NHEXAS), if these data are available.

### **3.6 Comments on Chapter 6 to Chapter 9**

The panelists did not specifically discuss topics in Chapters 6 through 9 of the profile. It should be noted that ATSDR received very few public comments on Chapters 6 and 7, and no public comments on Chapters 8 and 9. However, one panelist mentioned a paper by Brock et al., 1996, in the Journal of Analytical Toxicology, which outlines a specific approach for determining PCBs and pesticides in serum using capillary gas chromatography with electron capture detection.

### **3.7 Comments on Appendix A—ATSDR Minimal Risk Levels and Worksheets**

The panelists discussed at length the scientific basis of ATSDR's proposed approach for deriving MRLs for PCBs. The draft toxicological profile includes only a chronic oral MRL (0.02 µg/kg/day), which is based on immunological effects observed in rhesus monkeys. Before the panelists commented on the MRL for PCBs, ATSDR distributed handouts that define the MRL and how it is typically derived, including how uncertainty factors enter into MRL derivations. After the panelists reviewed this information, they discussed many topics relevant to the MRL for PCBs.

Overall, the panelists' discussion raised several important issues. First, though the panelists generally approved of ATSDR's derivations of the MRL based on the Tryphonas study (see Section 3.7.1 of this report), they highly recommended that ATSDR consider the human studies reviewed by Tilson et al. (1990) as a supplemental basis for the MRL. This study is reviewed in Section 3.7.2, below. Moreover, the panelists recommended that ATSDR consider an additional animal study as a basis for developing an intermediate oral MRL. Section 3.7.3 of this report summarizes their discussion regarding this study by Dr. Deborah Rice. Section 3.7.4 then reviews general comments the panelists made when discussing MRLs for PCBs, including mention of an additional human study that could be used to derive the MRL, but was not reviewed extensively during this discussion.

As reviewed below, the panelists suggested ATSDR conduct evaluations of studies in addition to the Tryphonas study to support the proposed MRL. Specifically, the panelists presented some information suggesting that neurological endpoints might be more sensitive than immunological endpoints and therefore a more appropriate basis for the MRL. The panelists reached no conclusions on this hypothesis, though, due to recognized limitations in the human studies reviewed by Tilson et al. (1990) and questions regarding ATSDR's use of uncertainty factors. Nonetheless, *the panelists underscored the fact that the dose-response data from two considerably different studies (and possibly more) paint a very consistent picture regarding health-guidance values for PCBs: An animal study and a*



human study, both of which considered different exposure doses and toxicological endpoints, suggest notably similar chronic oral MRL levels. The panelists recommended that ATSDR carefully evaluate the strengths and limitations of both studies before proposing its final chronic oral MRL for PCBs.

The observers made no comments on the panelists' discussion of MRLs.

### 3.7.1 Tryphonas Study (Tryphonas et al. 1989, 1991b)

Before the panelists discussed the public comments on ATSDR's proposed MRL, the Chemical Manager for the Toxicological Profile for PCBs described how ATSDR derived the chronic oral MRL for PCBs from the research conducted by Dr. Helen Tryphonas. The Chemical Manager explained that this study examined immunological effects among female rhesus monkeys that were exposed to Aroclor 1254 for 55 months. In general, monkeys that received Aroclor 1254 doses as low as 0.005 mg/kg/day had significantly reduced levels of antibody production in responses to challenges of sheep red blood cell antigens, while monkeys that received no doses did not have impaired immune responses. Therefore, the study reported a lowest-observed-adverse-effect level (LOAEL) of 0.005 mg/kg/day. The Chemical Manager then explained why ATSDR proposed applying three uncertainty factors to this LOAEL to derive an MRL: The Agency used a factor of 10 to extrapolate the LOAEL to a no-observed-adverse-effect level (NOAEL); a factor of 3 to extrapolate from animal studies to humans; and a factor of 10 to account for human variability. Accounting for these factors, the Chemical Manager noted that ATSDR proposed a chronic oral MRL of 0.02 µg/kg/day.

Some panelists highlighted the strengths of the Tryphonas study. For instance, one panelist noted that the study used a relatively large sample size, especially when compared to other studies involving rhesus monkeys. Another panelist added that the Tryphonas study was very carefully controlled and provides data on immunological effects for a wide range of PCB doses, while controlling for confounding factors that are unavoidable in human studies (e.g., exposures to other persistent, bioaccumulative toxins). After extensive debate and discussion on the merits of this study, none of the panelists identified critical shortcomings of the Tryphonas study.

The expert panel subsequently reviewed the public comments that ATSDR received on this study, and Dr. Tryphonas herself provided key insights to her work. An overview of these comments, and the panelists' responses, follows:

- **Public Comment on the Improper Selection of Toxicologic Endpoint for the MRL.** Based on concerns regarding the Tryphonas study (as outlined below), one public comment suggested that ATSDR should not base its chronic oral MRL on the immunotoxicity of PCBs. None of the

panelists agreed with the Submitter's criticisms, and Dr. Tryphonas was particularly confident that the immunological endpoint was an appropriate basis for ATSDR's MRL. Dr. Tryphonas acknowledged that evidence of PCB-related immunotoxicity has not been closely monitored in human studies. Nonetheless, she noted that many human studies provide accounts of adverse immunological effects following exposures to PCBs. As examples, she highlighted findings of relevant human studies:

Children born to women in Michigan and Wisconsin who ate fish from the Great Lakes suffered from higher incidence of infections (primarily bacterial) during their first 4 months of life, when compared to other infants (Swain 1991); infants born to women who were exposed to Kanechlor 500 and Kanechlor 300 had a higher incidence of colds and other infections when compared to infants born to women who were not exposed to these Kanechlors (Hara 1985); and 6-year old children from the Yusho and Yu-Cheng incidents had a higher incidence of bronchitis and ear infections, thus suggesting an immunological impairment<sup>1</sup> (Chao et al. 1997; Rogan et al. 1988). Though she noted that the aforementioned human studies all have limitations preventing one from concluding that PCBs cause immunological effects in humans, Dr. Tryphonas felt that the combined evidence from these and other studies suggest that PCBs are indeed toxic to the human immune system and that basing the MRL on immunotoxic effects is entirely appropriate.

Another panelist agreed with Dr. Tryphonas' arguments. He added that his experience as a researcher for EPA on Aroclor 1254 has found that immunotoxicity is a critical adverse effect associated with exposure to PCBs. This panelist noted that the Levinskas study found a dose-response relationship for clinical manifestations of PCB-related immunotoxicity in rhesus monkeys (Levinskas et al. 1984). Based on this study and other studies, this panelist was also convinced that basing the MRL on immunotoxic effects was appropriate.

- **Public Comment on the Clinical Relevance of the Tryphonas Study.** One public comment suggested that ATSDR not base its MRL on the Tryphonas study because the observed immunological effects have little clinical relevance to humans. Dr. Tryphonas again disagreed, for

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<sup>1</sup> Dr. Tryphonas indicated that the children considered in the Yusho and Yu-Cheng incidents did not have abnormally low levels of natural killer (NK) cells or immunoglobulin. However, Dr. Tryphonas noted that the NK cell numbers do not necessarily correlate with the functional activity of the NK cells and that immunoglobulin levels typically are only lowered by "great insults" to the immune system. Therefore, she concluded that people with normal NK cell numbers and immunoglobulin levels might still have compromised immune function. Similarly, Dr. Tryphonas also explained why a study of immunotoxic effects in transformer repairmen found negative results (Emmett et al. 1988): She noted that this study's negative results were for *secondary* immune responses, and that examining changes in secondary responses might fail to identify important effects to the primary (humoral) response.

several reasons. First, she defended her choice of the sheep red blood cell antigen partly due to its widespread use in animal studies to characterize immunotoxic effects of pollutants. In fact, Dr. Tryphonas noted that during the November 1996 meeting of the “Ad Hoc Organization for Economic Cooperation and Development (OECD) Workshop on Immunotoxicity Testing,” the use of the plaque-forming cell assay, which uses the sheep red blood cell antigens, was unanimously proposed as the standard functional assay for the screening of chemicals for potential immunotoxic effects using animal models.

Second, Dr. Tryphonas indicated that other researchers have reported that immune responses to the sheep red blood cell antigen in animals are highly predictive of these animals’ responses to selected infectious agents (Luster et al. 1988, 1992). Moreover, her ongoing research on the immunotoxic effects of toxaphene has indicated that *Cynomolgus* monkeys have immune responses to the tetanus toxoid comparable to the responses to sheep red blood cells, thus providing evidence that animal responses to the sheep red blood cells might be clinically relevant to the toxins that humans encounter.

Finally, Dr. Tryphonas explained that the general mechanism of the primary immune response to the sheep red blood cells in rhesus monkeys (e.g., uptake and processing of the antigen by macrophages, presentation of the antigen fragments to T lymphocytes, and subsequent production of specific antibodies by the B lymphocytes) is similar to the humoral response expected to occur in humans. However, noting that researchers will likely never conduct human testing with sheep red blood cells, Dr. Tryphonas acknowledged that the clinical relevance of humans’ immune response to sheep red blood cell antigens can only be hypothesized and not quantified.

For these reasons, Dr. Tryphonas believed that the implications of her research are clinically relevant to humans. Other panelists did not comment on this topic.

- **Public Comments that Rhesus Monkeys are a Poor Model of PCB Toxicity in Humans.** Two public comments argued that rhesus monkeys and humans have different metabolic pathways for PCBs, which, in turn, lead to different health effects in exposed rhesus monkeys and humans. The Submitters thus concluded that the immunologic effects observed in rhesus monkeys might be completely irrelevant to humans. None of the panelists agreed with this comment, as described below.

First, Dr. Tryphonas discussed the Submitters’ assertion that rhesus monkeys are more sensitive to PCBs than humans. Noting that this comment on sensitivity is apparently based on information

documented in an abstract (“Gillis and Price, 1996”), and not in the peer-reviewed literature, Dr. Tryphonas questioned the validity of the assertion. On another note, Dr. Tryphonas did not agree that pathways for PCB metabolism differ qualitatively between rhesus monkeys and humans, as one Submitter suggests. In fact, according to research carried out in monkeys (Arnold et al. 1993), Dr. Tryphonas indicated that the congener profile of PCBs measured in rhesus monkeys that were administered orally a mixture of PCB congeners typically found in human breast milk tends to match closely the profile observed in human blood (Kreiss 1995) and human breast milk (Dillon et al. 1981). Even if qualitative metabolic differences existed, however, Dr. Tryphonas still cautioned that they would not necessarily imply that rhesus monkeys are somehow more sensitive to PCBs than humans.

Other panelists provided additional insight on this public comment. For instance, based on the studies reviewed by Tilson et al. (1990) (see Section 3.7.2, below), one panelist noted that published research has suggested that rhesus monkeys might actually be less sensitive than humans for developing PCB-related health effects—in this case, behavioral or neurodevelopmental effects. Another panelist agreed, and added that his experience reviewing animal studies has not suggested a considerable sensitivity among rhesus monkeys to PCBs.

- **Public Comment on the Proposed Uncertainty Factors for the MRL.** One public comment suggested that the chronic oral MRL for PCBs should be based only on an overall uncertainty factor of 30, instead of 300.<sup>2</sup> Noting that her study examined immunological effects only among middle-aged rhesus monkeys, Dr. Tryphonas advocated the use of conservative uncertainty factors for deriving the MRL, since certain human groups—children, the elderly, and immunosuppressed populations—might be much more susceptible to PCB-related immunological effects; she thought an uncertainty factor of 300 was appropriate. Another panelist agreed, and recommended the Agency continue to use an overall uncertainty factor of at least 300; yet another panelist thought a case could be made for applying an additional uncertainty factor of 10 (for a total factor of 3,000) to account for children’s susceptibility. On the other hand, because the Tryphonas study considered some elderly rhesus monkeys, one panelist added that a case can be made for using less conservative uncertainty factors.

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<sup>2</sup> Technically, the Submitter’s recommendation was that the MRL should be based on the dermal, ocular, and nail effects observed in the rhesus monkeys of the Tryphonas study. The Submitter proposed using an uncertainty factor of 30 for an MRL based on that endpoint. However, the panelists’ comments focused on the use of uncertainty factors for the endpoint of immunological effects. In response to an earlier comment, the panelists agreed that basing the MRL on immunological effects was appropriate.

- **Public Comment on the Representativeness of an MRL Based on Exposure to Aroclor 1254.**  
One Submitter noted that the Tryphonas study used doses of unweathered Aroclor 1254, rather than doses of weathered PCBs, like those typically observed in the environment. Speculating that weathered PCBs are more toxic than the unweathered mixtures, this Submitter thought the MRL based on the Tryphonas study might understate risks of ingesting PCBs. Disagreeing with the Submitter's reasoning, one panelist did not think the available environmental sampling and toxicological data supported a blanket judgment that weathered PCBs in the environment are indeed more toxic than unweathered Aroclor 1254. As a result, this and another panelist did not agree with the Submitter's comment. No other panelists commented on this issue.

### 3.7.2 Studies Reviewed by Tilson et al. (1990)

Dr. Walter Rogan recommended that ATSDR consider deriving its MRL based on the findings of the studies reviewed by Tilson et al., which included Dr. Rogan as a contributing author (Tilson et al., 1990). This study examined neurodevelopmental effects in cohorts of children in Michigan and North Carolina and reported a NOAEL for 95 percent of the cohort of 0.093  $\mu\text{g}/\text{kg}/\text{day}$ —a NOAEL that represents the estimated daily dose that mothers can receive before adverse neurodevelopmental effects are observed in their offspring. The mothers in this study were not exposed to PCBs in occupational settings. Before the panelists commented on this recommendation, Dr. Rogan briefly reviewed key aspects of the studies reviewed by Tilson et al. (1990).

Dr. Rogan explained that this study used various metrics (e.g., the Brazelton Neonatal Behavioral Assessment Scale or the Bayley Scales of Infant Development) to determine whether children in the two cohorts developed normally or abnormally. Based on the motor development index, which quantifies children's abilities to stack blocks, dump raisins out of bottles, and so on, Dr. Rogan found that the children whose mothers had PCB concentrations in breast milk fat of 3.4 ppm or greater had statistically significant lower test results than the other children in the cohorts. In short, the breast milk fat concentration of 3.4 ppm was the highest PCB level in mothers below which no adverse health effects were observed in their children. This general trend was reportedly observed among the children at age 6 months, 12 months, 18 months, and 24 months, and was also observed for various other developmental metrics (e.g., IQ data). In fact, Dr. Rogan indicated that decreased visual recognition memory actually occurred among children whose mothers' breast milk fat concentration was 1.0 ppm, but this metric was used only in the Michigan cohort and not in the North Carolina cohort.

Because PCB doses were not measured in the Michigan and North Carolina studies, the researchers had to estimate the daily exposure of PCBs that would result in a mother having a breast milk fat concentration of 3.4 ppm at the time of delivering a child. Dr. Rogan listed the computational steps

and assumptions that were made to estimate this dose. First, the researchers estimated that a 25 year old woman who weighed 60 kg, had 25 percent body fat, and had 3.4 ppm of PCBs in her breast milk, likely had an overall body burden of 51 mg of PCBs. Dr. Rogan indicated the assumptions that were made in this calculation, such as the concentration of PCBs in a woman's breast milk fat were assumed to be equal to the concentration of PCBs in the fat throughout the rest of the body. Second, assuming that the 51 mg body burden is a result of a lifetime of low-level PCB exposure without any excretion, the researchers estimated that women with 3.4 ppm in their breast milk fat had an average daily PCB intake of 5.6  $\mu\text{g}/\text{day}$ . Normalizing this to the average body weight of a 25-year-old woman (60 kg), this daily intake translates into a daily dose of 0.093  $\mu\text{g}/\text{kg}/\text{day}$ —the dose that Dr. Rogan and his colleagues reported as a NOAEL for neurodevelopmental effects.<sup>3</sup>

Before the panelists commented on this study, Dr. Rogan listed several uncertainties associated with his dose calculations. First, because losses of PCBs through excretion, lactation, and metabolism were not factored into the dose calculations, the actual dose that results in 3.4 ppm of PCBs in breast milk fat would be higher than the reported NOAEL. Second, if dose calculations were based on women older than 25 years, the estimated daily dose would be lower than the reported NOAEL. Moreover, a difference in the analytical methods used in the Michigan study and the North Carolina study also might have caused the researchers to overestimate the actual NOAEL, possibly by a factor of 2.

Following this presentation, the panelists and ATSDR scientists discussed whether the studies reviewed by Tilson et al. (1990) can serve as an alternative basis for the chronic oral MRL. Some panelists noted that the data from the paper provide a very realistic account of environmental exposures, since the study considered humans who are exposed to low-level PCB doses through their everyday activities. However, other panelists highlighted corresponding limitations, such as the fact that the subjects in the Michigan and North Carolina studies were undoubtedly exposed to many other persistent, bioaccumulative toxins (e.g., dioxins) that might account, at least in part, for the observed health effects. In short, some panelists cautioned that one cannot be certain that the health effects resulted directly from PCB exposure, even though the study's evidence strongly suggests this is the case. Finally, some panelists recommended that ATSDR consider the uncertainties inherent in back-calculating exposure

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<sup>3</sup> The calculations described above can be summarized as:

$$\begin{aligned}\text{Body Burden} &= (\text{Body Weight}) \times (\text{Body Fat Percentage}) \times (\text{PCB Concentration in Fat}) \\ &= (60 \text{ kg}) \times (25\%) \times (3.4 \text{ mg PCB/kg fat}) \\ &= 51 \text{ mg PCBs}\end{aligned}$$

$$\begin{aligned}\text{Dose (NOAEL)} &= (\text{Body Burden}) / (\text{Assumed Exposure Duration}) / (\text{Body Weight}) \\ &= (51 \text{ mg PCBs}) / (25 \text{ years} \times 365 \text{ days/year}) / (60 \text{ kg}) \\ &= 0.000093 \text{ mg/kg/day} \\ &= 0.093 \mu\text{g/kg/day}\end{aligned}$$

doses when considering the studies reviewed by Tilson et al. (1990) as a basis for the chronic oral MRL—a potential shortcoming that does not apply to the carefully controlled animal studies.

Some panelists debated which uncertainty factors should be applied to the reported NOAEL to derive an MRL. Some suggested using only a factor of 10 to account for intra-species variability, but others suggested using an additional factor of 10 to account for children as a sensitive population. As Section 3.7.4 notes, the panelists discussed the applicability of this additional factor at length, but did not agree on the appropriateness of this factor for deriving an MRL. Despite these debates, several panelists noted that the NOAEL reported in the Tilson et al. 1990 paper (0.1  $\mu\text{g}/\text{kg}/\text{day}$ , when rounded to one significant digit) is comparable to ATSDR's extrapolation of a NOAEL in humans from the Tryphonas study (0.2  $\mu\text{g}/\text{kg}/\text{day}$ ).<sup>4</sup> Recognizing the similarity in these levels, some panelists thought ATSDR should stress that its final MRL can be defended both by considering immunological effects in rhesus monkeys and neurodevelopmental effects in humans. In other words, some panelists recommended that ATSDR use a weight-of-evidence approach in developing its MRL.

Regardless of whether ATSDR eventually adopts the studies reviewed by Tilson et al. (1990) as the basis for its MRL, the panelists suggested that the NOAEL dose from the North Carolina study should at least be cited in the toxicological profile's LSE tables.

### 3.7.3 Rice Studies

Several panelists and the Submitter of a public comment suggested that ATSDR consider the findings from Dr. Deborah Rice's recent studies on behavioral effects in monkeys as a basis for an intermediate oral MRL (Rice, 1999a; 1999b). These panelists briefly summarized Dr. Rice's study, which reportedly considered doses of mixtures of PCBs at 7.5  $\mu\text{g}/\text{kg}/\text{day}$  for 20 weeks to infant monkeys. According to the panelists, this dose level is comparable to that which can be observed environmentally. The monkeys were then tested for various behavioral effects at ages of 2.5 and 5 years. According to the panelists familiar with this research, Dr. Rice's study observed that the exposed monkeys had significant

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<sup>4</sup> Two notes deserve mention. First, Dr. Rogan provided evidence that his NOAEL might be overstated by a factor of two, due to the use of an analytical method that is known to overstate PCB concentrations. As a result, a NOAEL of 0.05  $\mu\text{g}/\text{kg}/\text{day}$  can be reported for the studies reviewed by Tilson et al. (1990) for the most sensitive population (i.e., embryos and children). (Note, some panelists thought an additional factor of 10 should be applied to his NOAEL to account for sensitive populations, but other panelists disagreed.) Second, the extrapolated NOAEL for the Tryphonas study was derived as follows: The LOAEL in rhesus monkeys of 5  $\mu\text{g}/\text{kg}/\text{day}$  was divided by a factor of 10 to convert the LOAEL to a NOAEL of 0.5  $\mu\text{g}/\text{kg}/\text{day}$  in monkeys. This NOAEL was then divided by 3 to account for interspecies variation. Therefore, ATSDR calculated the NOAEL in the non sensitive human population as 0.166  $\mu\text{g}/\text{kg}/\text{day}$ , rounded up to 0.2  $\mu\text{g}/\text{kg}/\text{day}$ . To account for the most sensitive population, such as the developing embryo and fetuses, ATSDR divided the 0.2  $\mu\text{g}/\text{kg}/\text{day}$  by a factor of 10 and resulted in an MRL of 0.02  $\mu\text{g}/\text{kg}/\text{day}$ . As a result, ATSDR's MRL (i.e., 0.02  $\mu\text{g}/\text{kg}/\text{day}$ ) is lower than the NOAEL in the most sensitive human subpopulation reported in the studies reviewed by Tilson et al. (1990) (i.e., 0.05  $\mu\text{g}/\text{kg}/\text{day}$ ).

behavioral deficits in numerous cognitive tests. These deficits include, but are not limited to, slowed learning and decreased performance on delayed spatial learning and memory tests.

Several panelists thought this study provides an adequate basis for deriving an MRL. Specifically, since the duration of exposure in this particular study was 20 weeks, the panelists noted that Dr. Rice's findings are an appropriate basis for an intermediate oral MRL.

#### 3.7.4 Additional Comments on MRLs

In addition to the specific comments on the Tryphonas study, the Tilson review, and the Rice study, the panelists addressed several other issues pertaining to MRLs for PCBs, as summarized below:

- **Consideration of the Dutch Cohort Studies as an Alternative Basis for the Chronic Oral MRL.** Several panelists thought ATSDR should consider basing its chronic oral MRL on data recently published for the Dutch cohorts (Huisman et al. 1995; Koopman-Esseboom et al. 1994, 1996a, 1996b; Lanting et al. 1998a, 1998b, 1998c, 1998d; Pantandin et al. 1997, 1998a, 1998b, 1998c, 1998d, 1999a, 1999b; Weisglas-Kuperus 1998). Though the panelists did not specify which endpoint was found to be most sensitive in these cohorts, one panelist thought the Agency might be able to develop dose-response relationships for thyroid effects among the subjects.

When reviewing the Dutch cohort study, some panelists identified a critical potential confounding factor: The human subjects were exposed to many chemicals of concern, including persistent, bioaccumulative toxins other than PCBs (e.g., dioxins). One panelist noted that the Dutch study reported that some adverse effects correlated with the combined exposure of dioxins and PCBs, while other effects correlated strictly with PCB exposures. As an example, this panelist indicated that learning effects among 4-year-olds were found to be PCB-specific. Several panelists agreed that working with the combined exposures to PCBs and dioxin might be complicated, but these panelists suggested that ATSDR should at least investigate the relevance of the data from the Dutch cohort studies for developing a chronic oral MRL.

- **Public Comment on Carcinogenic Effects and MRLs.** A public comment suggested that ATSDR's failure to consider carcinogenic effects when developing the MRL was "a mistake or serious oversight." ATSDR scientists explained that the MRLs, by definition, do not account for cancer effects. The panelists discussed at length various pros and cons of this approach—a discussion that focused primarily on ATSDR's health guideline policies and not specifically on PCBs, and is therefore not summarized in this report.



- **Use of Uncertainty Factors that Account for Children's Exposures.** Several panelists asked about the need for including additional uncertainty factors that account for childrens' sensitivity to PCB exposures. ATSDR scientists explained that the Agency's mandate is to *consider* use of such additional factors when developing health guidance values (i.e., the Agency is not *required* to use these factors) and that the origin of this mandate was for evaluating pesticide chemical residues, and not for PCBs. Nonetheless, some panelists recommended that ATSDR consider applying an additional uncertainty factor of 10 to the proposed MRL to protect children. Other panelists disagreed, noting that the uncertainty factor of 10 for intra-species variability was sufficient for this purpose.
- **Public Comment on an MRL Based on Other Endpoints.** One public comment suggested that ATSDR consider basing its chronic oral MRL on the reproductive and developmental effects observed in an animal study by Arnold (Arnold et al. 1995). The Submitter argued that the results of this study suggest an MRL of 0.5 µg/kg/day. None of the panelists advocated the use of this MRL, presumably because the MRLs based on the studies discussed in Sections 3.7.1 and 3.7.2 are both considerably lower than the MRL derived using the Arnold study.



#### 4.0 REFERENCES

- Anderson LM, Fox SD, Riggs CW, et al. 1993. Selective retention of polychlorinated biphenyl congeners in lung and liver after single-dose exposure of infant mice to Aroclor 1254. *J Environ Pathol Toxicol Oncol* 12(1):3-16.
- Anderson LM, van Havere K, Budinger JM. 1983. Effects of polychlorinated biphenyls on lung and liver tumors initiated in suckling mice by N-nitrosodimethylamine. *J Natl Cancer Inst* 71:157-163.
- Anderson LM, Ward JM, Fox SD, et al. 1986. Effects of a single dose of polychlorinated biphenyls to infant mice on N-nitrosodimethylamine-initiated lung and liver tumors. *Int J Cancer* 38:109-116.
- Arnold, DL, Bryce F, Karpinski K, et al. 1993. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (*Macaca mulatta*) monkeys. Part 1B. Prebreeding phase: clinical and analytical laboratory findings. *Food Chem Toxicol* 31(11):811-824.
- Arnold DL, Bryce F, McGuire PF, et al. 1995. Toxicological consequences of Aroclor 1254 ingestion by female rhesus (*Macaca mulatta*) monkeys. Part 2. Reproduction and infant findings. *Food Chem Toxicol* 33:457-474.
- Arnold DL, Nera EA, Stapley R, et al. 1996. Prevalence of endometriosis in Rhesus (*Macaca mulatta*) monkeys ingesting PCB (Aroclor 1254): Review and evaluation. *Fundamental and Applied Toxicology* 31(1):42-55.
- Bahn AK, Grover P, Rosenwaike I, et al. 1977. PCB and melanoma [Letter]. *N Engl J Med* 296:108.
- Bahn AK, Rosenwaike I, Herrmann N, et al. 1976. Melanoma after exposure to PCB's [Letter]. *N Engl J Med* 295:450.
- Barsotti DA, Marlar RJ, Allen JR. 1976. Reproductive dysfunction in rhesus monkeys exposed to low levels of polychlorinated biphenyls (Aroclor 1248). *Food Cosmet Toxicol* 14:99-103.
- Betrazzi PA, Riboldi L, Pesatori A, et al. 1987. Cancer mortality of capacitor manufacturing workers. *Am J Ind Med* 11:165-176.
- Bove FJ; Slade, BA; Canady, RA. 1999. Evidence of Excess Cancer Mortality in a Cohort of Workers Exposed to Polychlorinated Biphenyls. *Journal of Occupational and Environmental Medicine* 41(9):739-741.
- Brouwer A, Longnecker MP, Birnbaum LS, et al. 1999. Characterization of potential endocrine-related health effects at low-dose levels of exposure to PCBs. *Environ Health Perspect Suppl* 107(4):639-649.
- Brown DP. 1987. Mortality of workers exposed to polychlorinated biphenyls -An update. *Arch Environ Health* 42(6):333-339.
- Brown DP, Jones M. 1981. Mortality and industrial hygiene study of workers exposed to polychlorinated biphenyls. *Arch Environ Health* 36:120-129.
- Chao W-Y, Hsu C-C, Guo YL. 1997. Middle-ear disease in children exposed prenatally to polychlorinated biphenyls and polychlorinated dibenzofurans. *Arch Environ Health* 52(4):257-262.

Chen RC, Tang SY, Miyata H, et al. 1985a. Polychlorinated biphenyl poisoning: Correlation of sensory and motor nerve conduction, neurologic symptoms, and blood levels of polychlorinated biphenyls, quaterphenyls, and dibenzofurans. *Environ Res* 37:340-348.

Chia LG, Chu FL. 1984. Neurological studies on polychlorinated biphenyl (PCB)-poisoned patients. *Am J Ind Med* 5:117-126.

Chia LG, Chu FL. 1985. A clinical and electrophysiological study of patients with polychlorinated biphenyl poisoning. *J Neurol Neurosurg Psychiatry* 48:894-901.

Dillon et al. 1981. *Food and Cosmetics Toxicology* 19:437-442.

Emmett EA, Maroni M, Jefferys, et al. 1988. Studies of transformer repair workers exposed to PCBs: II. Results of clinical laboratory investigations. *Am J Ind Med* 14:47-62.

Fischbein A, Rizzo JN, Solomon SJ, et al. 1985. Oculodermatological findings in workers with occupational exposure to polychlorinated biphenyls (PCBs). *Br J Ind Med* 42:426-430.

Gartner LW, Arias IM. 1966. Studies of prolonged neonatal jaundice in the breast-fed infant. *J Pediatr* 68:54.

Gerhard I, Daniel B, Link S, et al. 1998. Chlorinated hydrocarbons in women with repeated miscarriages. *Env Health Persp* 106:675-681.

Hara I. 1985. Health status and PCBs in blood of workers exposed to PCBs and their children. *Environ Health Perspect* 59:85-90.

Hansen LG. 1999. PCB congener weight% in Aroclors of 5 types. In: Hansen LG, ed. *The ortho side of PCBs: Occurrence and disposition*. Boston, MA: Kluwer Academic Publishers, 205.

Hardell L, Van Bavel B, Lindstrom G, et al. 1996. Higher concentrations of specific polychlorinated biphenyl congeners in adipose tissue from non-Hodgkin's lymphoma patients compared with controls without a malignant disease. *International Journal of Oncology* 9(4):603-608.

Helzlsouer KJ, Alberg AJ, Huang HY, et al. 1999. Serum concentrations of organochlorine compounds and the subsequent development of breast cancer. *Cancer Epidemiology, Biomarkers, and Prevention* 8:525-532.

Hsu C-C, Yu M-LM, Chen Y-CJ, et al. 1994. The Yu-Cheng rice oil poisoning incident. In: Schecter A, ed. *Dioxins and health*. New York, NY: Plenum Press, 661-684.

Hsu ST, Ma CI, Hsu SKH, et al. 1985. Discovery and epidemiology of PCB poisoning in Taiwan: A four-year followup. *Environ Health Perspect* 59:5-10.

Huisman M, Koopm-Esseboom C, Fidler V, et al. 1995. Perinatal exposure to polychlorinated biphenyls and dioxins and its effect on neonatal neurological development. *Early Hum Dev* 41:111-127.

Hunter DJ, Hankinson SE, Laden F, et al. 1997. Plasma organochlorine levels and the risk of breast cancer. *N Engl J Med* 337:1253-1258.

Jacobson JL, Jacobson SW. 1996a. Intellectual impairment in children exposed to polychlorinated biphenyls in utero. *N Engl J Med* 335:783-789.

- Jacobson JL, Jacobson SW. 1996b. Dose-response in perinatal exposure to polychlorinated biphenyls (PCBs): The Michigan and North Carolina cohort studies. *Toxicol Ind Health* 12(3/4):435-445.
- Jacobson JL, Jacobson SW, Humphrey HEB. 1990a. Effects of in utero exposure to polychlorinated biphenyls and related contaminants on cognitive functioning in young children. *J Pediatr* 116:38-45.
- Jacobson JL, Jacobson SW, Schwartz PM, et al. 1984a. Prenatal exposure to an environmental toxin: A test of the multiple effects model. *Dev Psychol* 20:523-532.
- Jacobson SW, Fein GG, Jacobson JL, et al. 1985. The effect of intrauterine PCB exposure on visual recognition memory. *Child Dev* 56:853-860.
- Kimbrough RD, Doemland ML, LeVois ME. 1999. Mortality in male and female capacitor workers exposed to polychlorinated biphenyls. *Journal of Occupational and Environmental Medicine* 41:161-171.
- Koopman-Esseboom C, Huisman M, Weisglas-Kuperus N, et al. 1994. PCB and dioxin levels in plasma and human milk of 418 Dutch women and their infants. Predictive value of PCB congener levels in maternal plasma for fetal and infant's exposure to PCBs and dioxins. *Chemosphere* 28(9):1721-1732.
- Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MAJ, et al. 1996a. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. *Pediatrics* 97:700-706.
- Koopman-Esseboom C, Weisglas-Kuperus N, de Ridder MAJ, et al. 1996b. Effects of polychlorinated biphenyl/dioxin exposure and feeding type on infants' mental and psychomotor development. *Pediatrics* 97(5):700-706.
- Kreiss, K. 1985. Studies on populations exposed to polychlorinated biphenyls. *Environ Health Perspect* 60:193-199.
- Kuratsune M, Nakamura Y, Ikeda M, et al. 1987. Analysis of deaths seen among patients with Yusho- A preliminary report. *Chemosphere* 16:2085-2088.
- Lanting CI, Fidler V, Huisman M, et al. 1998a. Determinants of polychlorinated biphenyls levels in plasma from 42-month-old children. *Arch Environ Contam Toxicol* 35:135-139.
- Lanting CI, Huisman M, Muskiety FAJ, et al. 1998b. Polychlorinated biphenyls in adipose tissue, liver, and brain from nine stillborns of varying gestational ages. *Pediatr Res* 44(2):222-225.
- Lanting CI, Patandin S, Fidler V, et al. 1998c. Neurological condition in 42-month-old children in relation to pre- and postnatal exposure to polychlorinated biphenyls and dioxins. *Early Hum Dev* 50:283-292.
- Lanting CI, Patandin S, Weisgals-Kuperus N, et al. 1998d. Breastfeeding and neurological outcome at 42 months. *Acta Paediatr* 87:1224-1229.
- Leeder JS, Kearns GL. 1997. Pharmacogenetics in pediatrics: implications for practice. *Pediatric Clinics of North America* 44:55-77.
- Levinskas GJ, Martin DP, Seibold HR, et al. 1984. Aroclor 1254: Reproduction study with Rhesus monkeys (*macaca mulatta*). [Unpublished study]

- Lonky E, Reihman J, Darvill T, et al. 1996. Neonatal behavioral assessment scale performance in humans influenced by maternal consumption of environmentally contaminated Lake Ontario fish. *J Great Lakes Res* 22(2):198-212.
- Loomis D, Browning SR, Schenck AP, Gregory E, Savitz DA. 1997. Cancer mortality among electric utility workers exposed to polychlorinated biphenyls. *Occup Environ Med* 54(10):720-8.
- Luster MI, Munson AE, Thomas PT, et al. 1988. Development of a testing battery to assess chemical-induced immunotoxicity: National Toxicology Program's guidelines for immunotoxicity evaluation in mice. *Fundam Appl Toxicol* 10:2-9.
- Luster MI, Portier C, Pait DG, et al. 1992. Risk assessment in immunotoxicology: I. Sensitivity and predictability of immune tests. *Fundam Appl Toxicol* 18:200-210.
- Masuda Y. 1994. The Yusho rice oil poisoning incident. In: Schecter A., ed. *Dioxins and health*. New York, NY: Plenum Press, 633-659.
- Mayes BA, McConnell EE, Neal BH, et al. 1998. Comparative carcinogenicity in Sprague-Dawley rats of the polychlorinated biphenyl mixture aroclors 1016, 1242, 1254, and 1260. *Toxicol Sci* 41(1):62-76.
- Mendola P, Buck GM, Sever LE, et al. 1997. Consumption of PCB-contaminated freshwater fish and shortened menstrual cycle length. *American Journal of Epidemiology* 146(11):955-960.
- Nagayama J, Iida T, Hirakawa H, et al. 1997. Effects of lactational exposure to chlorinated dioxins and related chemicals on thyroid functions in Japanese babies. *Organohalogen Compounds* 33:446-450.
- Paneth N. 1991. Human reproduction after eating PCB-contaminated fish. *Health Environ Digest* 5:4-6.
- Pantaleoni G, Fanini D, Sponta AM, et al. 1988. Effects of maternal exposure to polychlorinated biphenyls (PCBs) on F1 generation behavior in the rat. *Fund Appl Toxicol* 11:440-449.
- Patandin S, Weiglas-Kuperus N, de Ridder MAJ, et al. 1997. Plasma polychlorinated biphenyl levels in Dutch preschool children either breast-fed or formula-fed during infancy. *Am J Public Health* 87:1711-1714.
- Patandin S, Dagnelie PC, Mulder PGH, et al. 1998a. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: A comparison between breast-feeding, toddler, and long-term exposure. *Environ Health Perspect* 107:45-51.
- Patandin S, Dagnelie PC, Weisglas-Kuperus N, et al. 1998b. Exposure to PCBs, PCDDs and PCDFs through breast milk compared with long-term dietary exposure. *Organohalogen Compounds* 38:214A-214F.
- Patandin S, Koopman-Esseboom C, De Ridder MAJ, et al. 1998c. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. *Pediatr Res* 44(4):538-545.
- Patandin S, Koopman-Esseboom C, De Ridder MAJ, et al. 1998d. Effects of environmental exposure to polychlorinated biphenyls and dioxins on birth size and growth in Dutch children. *Pediatr Res* 44(4):538-545.
- Patandin S, Dagnelie PC, Mulder PGH, et al. 1999a. Dietary exposure to polychlorinated biphenyls and dioxins from infancy until adulthood: A comparison between breast-feeding, toddler, and long-term exposure. *Environ Health Perspect* 107:45-51.

Patandin S, Lanting CI, Mulder PGH, et al. 1999b. Effects of environmental exposure to polychlorinated biphenyls and dioxins on cognitive abilities in Dutch children at 42 months of age. *J Pediatr* 134:33-41.

Pessah IN. 1997. Non-coplanar PCBs alter neuronal Ca<sup>2+</sup> regulation and neuroplasticity by a FKBP12/ryanodine receptor-mediated mechanism. *Toxicologist* 36:333.

Rao CV, Banerji SA. 1993. Effect of polychlorinated biphenyls (Aroclor 1260) on histology of adrenal of rats. *J Environ Biol* 14:1-6.

Rice DC. 1999a. Behavioral impairment produced by low-level postnatal PCB exposure in monkeys. *Environ Res* 80:S113-S121.

Rice DC. 1999b. Effect of exposure to 3,3',4,4',5-pentachlorobiphenyl (PCB 126) throughout gestation and lactation on development and spatial delayed alternation performance in rats. *Neurotoxicol Teratol* 21(1):59-69.

Rogan WJ, Gladen BC. 1991. PCBs, DDE, and child development at 18 and 24 months. *Ann Epidemiol* 1(5):407-413.

Rogan WJ, Glad BC, Hung KL, et al. 1988. Congenital poisoning by polychlorinated biphenyls and their contaminants in Taiwan. *Science* 241:334-336.

Rogan WJ, Gladen BC, McKinney JD, et al. 1986. Neonatal effects of transplacental exposure to PCBs and DDE. *J Pediatr* 109:335-341.

Rothman N, Canter KP, Blair A, et al. 1997. A nested case-control study of non-Hodgkin lymphoma and serum organochlorine residues. *Lancet (British Edition)* 350(9073):240-244.

Schantz SL. 1996. Developmental neurotoxicity of PCBs in humans: What do we know and where do we go from here? *Neurotoxicol Teratol* 18(3):212-27, 229-76.

Sinks T, Steele G, Smith AB, et al. 1992. Mortality among workers exposed to polychlorinated biphenyls. *Am J Epidemiol* 136(4):389-398.

Smith AB, Schloemer J, Lowry LK, et al. 1982. Metabolic and health consequences of occupational exposure to polychlorinated biphenyls. *Br J Ind Med* 39:361-369.

Stewart P, Darvill T, Lonky E, et al. 1999. Assessment of prenatal exposure to PCBs from maternal consumption of Great Lakes fish: An analysis of PCB pattern and concentration. *Environ Res* 80:S87-S96.

Swain WR. 1991. Effects of organochlorine chemicals on the reproductive outcome of humans who consumed contaminated Great Lakes fish: An epidemiologic consideration. *J Toxicol Environ Health* 33:587-639.

Tilson et al. 1990. Polychlorinated Biphenyls and the Developing Nervous System: Cross-Species Comparisons. *Neurotoxicology and Teratology* 12:239-248.

Tryphonas H, Hayward S, O'Grady L, et al. 1989. Immunotoxicity studies of PCB (Aroclor 1254) in the adult rhesus (*Macaca mulatta*) monkey—preliminary report. *Int J Immunopharmacol* 11:199-206.

Tryphonas H, Luster MI, Schiffman G, et al. 1991b. Effect of chronic exposure of PCB (Aroclor 1254) on specific and low specific immune parameters in the rhesus (*Macaca mulatta*) monkey. *Fund Appl Toxicol* 16:773-786.

Weiglas-Kuperus N. 1998. Neurodevelopmental, immunological and endocrinological indices of perinatal human exposure to PCBs and dioxins. *Chemosphere* 37(9-12):1845-1853.

Winneke G, Bucholski A, Heinzow B, et al. 1998. Developmental neurotoxicity of polychlorinated biphenyls (PCBs): cognitive and psychomotor functions in 7-month old children. *Toxicol Lett* 102-103:423-428.

Wong PW, Pessah IN. 1996. *Ortho*-substituted polychlorinated biphenyls alter calcium regulation by a ryanodine receptor-mediated mechanism: structural specificity toward skeletal- and cardiac-type microsomal calcium release channels. *Mol Pharmacol* 49:740-751.

Wong PW, Pessah IN. 1997. Noncoplanar PCB 95 alters microsomal calcium transport by an immunophilin FKBP12-dependent mechanism. *Mol Pharmacol* 51:693-702.



**APPENDIX A**  
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**APPENDIX B**

**AGENDA**

## **Agenda for the Expert Panel Review of the Toxicological Profile for PCBs**

**September 27, 1999**

### **Morning Session**

- 10:00 Meeting convenes  
Welcome and Introduction:  
Dr. Henry Falk, Assistant Administrator, ATSDR
- Review of Agenda and Meeting Objectives:  
Dr. Christopher T. De Rosa, Director, Division of Toxicology
- 10:15 Developmental Effects (Chapter 2)

12:00 **Lunch**

### **Afternoon Session**

- 1:00 Continue Developmental Effects Discussion
- 2:00 Neurobehavioral, Neurodevelopmental, Children (Chapter 2)
- 3:15 Break
- 3:30 Endocrine Disruption (Chapter 2)
- 5:00 Adjourn Meeting

**September 28, 1999**

**Morning Session**

8:30 Discussion of Other Health Effects

- Reproductive
- Dermal
- Respiratory
- Other

10:30 Discussion of Chronic Oral MRL and Immunological Effects

- Comparison of studies' merits as critical MRL study
- Appropriateness of study end-points for use in MRL derivation
- Potential confounders in epidemiologic studies
- Applicability\comparison of end-points across studies
- Critical effects and uncertainty factor selection
- Animal Sensitivities
- Congeners
- PCB planar vs coplanar
- Dioxin-like; phenobarbital-like; estrogen-like PCBs
- Other issues

12:00 **Lunch**

**Afternoon Session**

1:15 Discussion of the Following Cancer Issues:

- Weight-of-the-evidence
- Breast Cancer
- GIT Cancer
- Non-Hodgkins Lymphoma
- Hepatocellular Carcinoma
- Melanoma and Squamous Cell Carcinoma
- Yusho and Yu-Cheng incidents and cancer

2:30 Break

2:45 Continue Cancer Discussion

5:00 Adjourn meeting

**September 29, 1999**

**Morning Session**

8:30 Review of Chemical and Physical Information (Chapter 3)  
Response to Public Comments

9:15 Review of Production, Import, Use and Disposal (Chapter 4)

9:45 Review of Potential for Human Exposure (Chapter 5)

10:30 Review of Analytical Methods (Chapter 6) and Other Issues

11:15 Break

11:30 Discussion of Public Health Statement (Chapter 1)  
Response to public comments regarding general issues

12:00 - 12:30 Wrap-up and Next Steps

