

ATTACHMENT N

Evaluation of Uncertainty Factors in Non-Cancer Reference Dose for PCBs (Aroclor 1254)

Introduction

The Reference Dose (RfD) is a standard tool used by the U.S. Environmental Protection Agency (EPA) to evaluate potential non-carcinogenic health hazards. According to its definition, daily exposure at or below the RfD is likely to be without appreciable risk of deleterious effects to the human population, including sensitive subgroups, over the course of a lifetime (EPA, 1988).

The RfD used in the Housatonic River Human Health Risk Assessment (HHRA) to assess the potential non-cancer effects of PCBs is the chronic RfD listed on EPA's Integrated Risk Information System (IRIS) for Aroclor 1254, which is 2×10^{-5} mg/kg-day (Vol. I, p. 2-13). This RfD is based on the results from a long-term dosing study of Rhesus monkeys (Arnold et al., 1993a,b; Tryphonas et al., 1989, 1991a,b), in which dermal, ocular, and immunological effects were observed in the monkeys at a dose level of 5×10^{-3} mg/kg-day. To derive a chronic RfD from these data, EPA applied several uncertainty factors (UFs) totaling 300, as discussed further below.

GE previously provided to EPA a detailed analysis, prepared by scientists at AMEC Earth & Environmental, showing that even using the same monkey study used by EPA to develop this RfD, two of the UFs used by EPA are overly conservative (AMEC, 2001). Based on replacing these two UFs with more appropriate values, a revised chronic RfD of 2×10^{-4} mg/kg-day was derived for Aroclor 1254. A summary of this analysis is presented in this Attachment.

Basis for EPA's Current Chronic RfD for Aroclor 1254

EPA's chronic RfD for Aroclor 1254 is based on the results of a five-year feeding study in Rhesus monkeys (Arnold et al., 1993a,b; Tryphonas et al., 1989; Tryphonas et al., 1991a,b). In that study, groups of 16 adult female monkeys ingested gelatin capsules containing Aroclor 1254 at daily doses of 0, 5, 20, 40, or 80 μ g/kg-day for over five years. PCB concentrations in the monkeys had achieved steady-state pharmacokinetics by 25 months of exposure, as demonstrated by PCB measurements in blood and adipose tissue (Tryphonas et al., 1989; Mes et al., 1989). The general health and clinical pathology findings were reported by Arnold et al. (1993a,b) after 37 months of exposure. Clinical signs of toxicity in the PCB-exposed adult female monkeys consisted of eye exudate, inflammation and/or prominence of the tarsal

(Meibomian) glands, and changes in finger and toe nails. Significant dose-related trends were reported for these clinical signs (Arnold et al., 1993a). The results of an immunologic assessment of the PCB-exposed adult female monkeys were reported by Tryphonas et al. (1989, 1991a,b) after 55 months of exposure. The most significant finding was a treatment-related decrease in antibody response (IgG, IgM) to sheep red blood cells (SRBC). The Lowest Observed Adverse Effect Level (LOAEL) for clinical signs and immune system effects was 5 µg/kg-day, or 5×10^{-3} mg/kg-day.

To derive its chronic RfD, EPA selected this LOAEL and then applied a total UF of 300. This UF was composed of: (a) a factor of 10 to account for inter-individual sensitivity; (b) a factor of 3 to account for the extrapolation from Rhesus monkeys to humans; (c) a factor of 3 to account for the use of a minimal-effect LOAEL rather than a NOAEL; and (d) a final factor of 3 to adjust for use of what was characterized as a subchronic study to derive a chronic RfD (EPA, 2003). This resulted in the chronic RfD of 2×10^{-5} mg/kg-day that is currently listed on EPA's IRIS database and is used in the Housatonic River HHRA.

As discussed below, review of the available evidence suggests that two of these specific UFs should be reduced.

The Inter-species UF

As noted above, in deriving the Aroclor 1254 RfD, EPA applied a UF of 3 for inter-species extrapolation. The basis for EPA's selection of a value of 3 rather than 10 was the assumption of broadly similar physiological and metabolic processes between primates and humans (EPA, 2003). It was based on the premise that the UF of 3 would afford protection to humans when relying upon data derived from primates. Although this assumption appears reasonable at first inspection, a species comparison of exposure and health effects data for PCBs suggests that Rhesus monkeys are significantly more sensitive than humans to the non-cancer effects of PCBs, including the types of effects that were observed in the underlying study.

To begin with, it is generally recognized that Rhesus monkeys are more sensitive to the non-cancer effects of PCBs than are other animal models. EPA (2003) states that “[i]n general, Rhesus monkeys have shown adverse effects to PCB mixtures at doses 10-fold lower than in other species.” Similarly, the ATSDR (2000) *Toxicological Profile for PCBs* states (at p. 16):

Animal studies have shown that PCBs induce effects in monkeys at lower doses than in other species, and that immunological, dermal/ocular, and neurobehavioral changes are particularly sensitive indicators of toxicity in monkeys exposed either as adults, or during pre- or postnatal periods.

Moreover, reviews of the human epidemiological data in relation to the data on non-human primates have shown that Rhesus monkeys are likewise more sensitive than humans to the effects of PCBs (Tilson et al., 1990; Arnold et al., 1995).

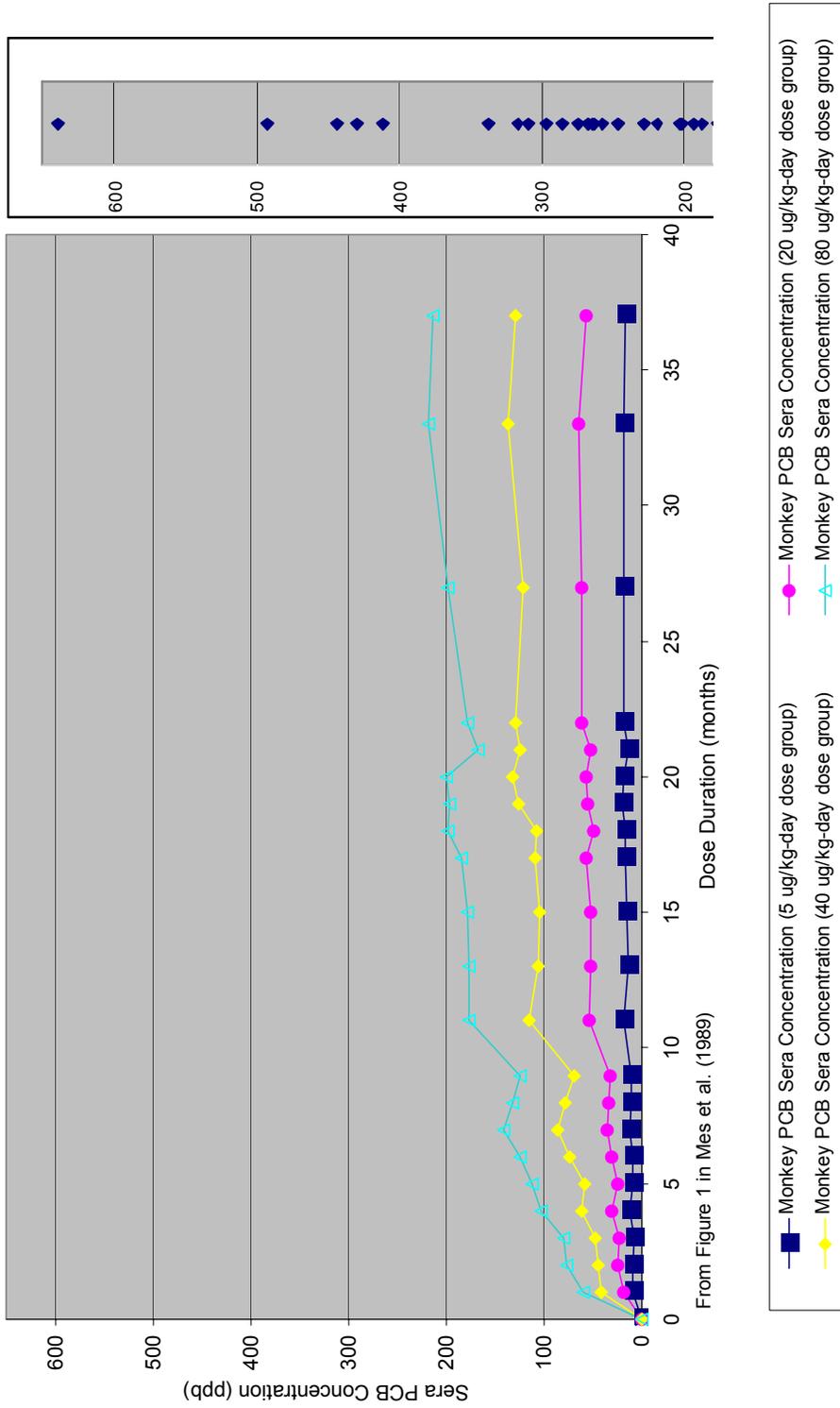
AMEC (2001) further demonstrated this by comparing PCB toxicity data in humans who had long-term occupational exposures with toxicity data on Rhesus monkeys from the same long-term study used to develop the RfD. The human data include a detailed examination of the individual medical histories and clinical evaluation records of 191 electrical capacitor workers who were a part of a medical surveillance program at GE plants in Hudson Falls and Fort Edward, NY, and who were very highly exposed to PCBs, including Aroclor 1254, in an occupational setting. These workers participated in a medical surveillance program in which blood serum levels of Aroclor 1254 were recorded for most participants (Lawton et al., 1981, 1985), thus enabling the clinical observations of each individual to be matched with his/her PCB body burden measurements. These comparisons allowed the determination of whether the PCB health effects observed in Rhesus monkeys were also observed at similar body burdens in the highly exposed human cohort.

All of these workers were employed (and PCBs were still in use) when the initial blood measurements were made in 1976. As part of the medical examination, workers were specifically checked for skin rashes, changes in pigmentation of the skin and nails, erythema and thickening of the skin, increased acne, swelling of eyelids, and abnormal secretions from the eyes. No evidence of dermal or ocular effects from PCB exposure was seen in the physical examinations. PCB use ceased in 1977, and follow-up PCB blood serum data were collected in 1979 (using an improved analytical technique) for 172 capacitor workers in the medical surveillance program. Blood serum levels for Aroclor 1254 from the 1979 data ranged from 4 to 639 ppb, with an arithmetic mean of 93 ppb. Although these data represent body burdens measured three years post-PCB use, approximately 85 percent of the blood levels were greater than 20 ppb, which, as described below, was equivalent to the lowest blood levels observed in the Rhesus monkey study.

Blood serum levels of Aroclor 1254 measured in the Rhesus monkey study (Tryphonas et al., 1989; Arnold et al., 1990, 1993a,b, 1995; Tryphonas, 1995) were compared to those measured in the GE capacitor workers, as shown graphically on Figure 1. Rhesus monkeys with serum concentrations ranging from 19 ppb (corresponding to the 5 µg/kg-day dose) to 218 ppb (80 µg/kg-day dose) of Aroclor 1254 displayed a number of readily observable dermal and ocular effects, including swelling of the Meibomian glands, swelling around the eyes, nail discoloration, and nail loss (Arnold et al., 1993a,b). However, as shown in this study of GE workers, humans with an average body burden for Aroclor 1254 of 93 ppb and as high as 639 ppb did not experience similar ocular and dermal effects. The absence of effects in the workers indicates that humans are less sensitive than Rhesus monkeys for these endpoints.

With respect to immunological effects, in contrast with the data on Rhesus monkeys, humans with average serum levels of approximately 9-12 ppb (with individual values as high as 300 ppb) have shown no adverse effects on the immune system as measured by cutaneous delayed hypersensitivity responses to mumps and trichophyton antigens (Emmett et al., 1988a,b). These tests, while not exactly comparable to those conducted in the Rhesus monkeys, are of great value in the overall assessment of immunocompetence, because interaction of the three principal cells of the immune system (macrophages, T-lymphocytes, and B-lymphocytes) is required for these responses to occur (Stites et al., 1994). Furthermore, if PCBs in concentrations of 10 ppb in serum result in loss of immune competence, as suggested by the monkey studies, individuals with substantially higher serum PCB concentrations should be at greater risk of morbidity and mortality from a variety of infectious diseases. This is not the case. Taylor (1988) conducted a mortality study of over 6,000 capacitor workers, including a group of workers in direct exposure areas with a geometric mean serum PCB concentration of 302 ppb. No increase in mortality attributable to infectious disease was observed in these workers. Levels of circulating immunocytes were often included among the batteries of clinical tests in studies of the health of PCB-exposed workers (Fischbein et al., 1979; Baker et al., 1990; Maroni et al., 1981a,b; Chase et al., 1982; Smith et al., 1982; Stark et al., 1986). None of these studies found an association between PCB exposure and leukocyte or differential blood counts. In short, while immunological effects were observed in the Rhesus monkeys, such effects have not been demonstrated in humans, even among individuals with blood concentrations nearly two orders of magnitude higher.

Figure 1. Human and Monkey Sera PCB Concentrations



Finally, the fact that mortality has been observed in monkeys exposed to PCBs and that mortality has not been observed in humans exposed to even higher levels of PCBs demonstrates the great difference in species sensitivity. In a study by Barsotti et al. (1976), one of nine monkeys treated with Aroclor 1248 at either 100 or 200 µg/kg-day died from toxicity during the course of the study. In a separate study, Tryphonas et al. (1986) noted that “[t]he results suggest that severe potentially fatal PCB toxicity can develop in rhesus monkeys following ingestion of Aroclor 1254 at 200 µg/kg-day for a period of 27 months or longer.” In a third study, three monkeys had to be euthanized due to severe PCB toxicity (Tryphonas et al., 1991a,b). The average blood PCB concentration in these animals after 55 months of treatment was 285 ppb. In contrast, studies of PCB-exposed workers found no evidence of increased mortality, even among groups of workers with average PCB concentrations of 400 ppb or more or among individuals with serum PCB levels as high as 3,250 ppb (Lawton et al., 1985; James et al., 1993).

In summary, a comparison of PCB serum data from studies of Rhesus monkeys and human worker cohorts suggests that the Rhesus monkey is at least one to two orders of magnitude more sensitive to the dermal, ocular, and immunologic effects of PCBs than are humans. In fact, it appears that PCBs are lethal to Rhesus monkeys at PCB serum levels that have no demonstrable effects in humans. Consequently, there is no basis for EPA’s assumption that a UF of 3 for inter-species extrapolation is necessary for developing an RfD to be protective of humans.

The Subchronic-to-Chronic UF

In deriving the current Aroclor 1254 RfD, EPA selected a subchronic-to-chronic UF of 3 to adjust for study duration. This factor is intended to account for uncertainties related to less-than-chronic exposure and assumes that longer exposure durations would result in more pronounced adverse health effects. However, the monkey study itself, as well as the human data from the GE workers, demonstrates that no adjustment for exposure duration is necessary in calculating the PCB RfD.

In the Rhesus monkey study, the monkeys were dosed for greater than 25 percent of their lifetimes and, as reported by Arnold et al. (1993a,b) and Tryphonas (1995), a qualitative pharmacokinetic equilibrium had been established in 90 percent of the monkeys with respect to PCB concentrations in adipose tissue and blood. This information indicates that the study

should be considered equivalent to a chronic study and that no adjustment for exposure duration is necessary in calculating the PCB RfD. In fact, in the IRIS listing for Aroclor 1254, EPA (2003) states that “the immunologic and clinical changes that were observed did not appear to be dependent upon duration” Other data in Rhesus monkeys show that dermal and ocular effects of PCBs are reversible and that health status improves as tissue levels decrease during a recovery period where dosing was terminated (Allen et al., 1980; Barsotti, 1980), suggesting that the non-cancer effects of concern for chronic PCB exposure are related to the concentration of PCBs in tissue or blood. Therefore, clinical health effects of PCB exposure would not be expected to worsen over time once PCB equilibrium is achieved.

In addition, the human data from the GE workers discussed above indicate that chronic exposure to PCBs does not result in dermal, ocular, or immune system effects. Of the 191 capacitor workers who were a part of the GE medical surveillance program, 126 workers had been exposed for seven years or more (greater than half of these workers actually had been exposed for 15 years or more). This determination was made by analyzing the employment history of each worker and discounting the time that each individual was not actively working with PCBs at the plant. EPA (1989) defines chronic exposure for humans as “duration from seven years to a lifetime.” The average PCB serum concentration for those workers with seven or more years of exposure was 120 ppb. These chronically exposed workers, however, showed no evidence of dermal, ocular or immunologic effects related to PCB exposure.

This information indicates that, in deriving an RfD from the Rhesus monkey study, there is no need for application of a subchronic-to-chronic UF, and thus that that factor can be set at 1.

Calculation of a Revised Chronic RfD for Aroclor 1254

Based on the above considerations, AMEC (2001) derived a revised chronic RfD for Aroclor 1254, using the same monkey study results used by EPA, but applying revised, empirically based UFs of 1 instead of 3 for inter-species extrapolation and for study duration, combined with the same other UFs used by EPA in developing its RfD. This procedure resulted in application of a total UF of 30, which yields a revised chronic RfD of 2×10^{-4} mg/kg-day – 10 times higher than the value for Aroclor 1254 established by EPA.

As discussed above, review of the data from the monkey study used by EPA to establish its RfD in relation to the clinical data and body burden measurements for the GE workers, as well as data from other human epidemiological studies of PCB exposure in highly exposed workers,

supports this adjustment of the UFs for inter-species extrapolation and study duration. As a result, GE believes that the revised chronic RfD of 2×10^{-4} mg/kg-day would be fully protective of human health and should serve as a reasonable and conservative default value for assessing potential non-cancer hazards from chronic exposure to PCBs in the Housatonic River HHRA.

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