Aroclor 1254; CASRN 11097-69-1

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Aroclor 1254

File First On-Line 10/01/1994

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	10/01/1994
Inhalation RfC (I.B.)	not evaluated	
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Aroclor 1254
CASRN — 11097-69-1
Primary Synonym — PCBs, Polychlorinated Biphenyls
Last Revised — 10/01/1994

The oral Reference Dose (RfD) is based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. It is expressed in units of mg/kg-day. In general, the RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Please refer to the Background Document for an elaboration of these concepts. RfDs can also be derived for the noncarcinogenic health effects of

substances that are also carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

I.A.1. Oral RfD Summary

Critical Effect	Experimental Doses*	UF	MF	RfD
Ocular exudate, inflamed and prominent Meibomian glands, distorted growth of finger and toe nails; decreased antibody (IgG and IgM) response to sheep erythrocytes **Monkey Clinical and Immunologic Studies** **Arnold et al., 1994a,b; Tryphonas et al., 1989, 1991a,b**	NOAEL: None LOAEL: 0.005 mg/kg-day	300	1	2E-5 mg/kg-day

* Conversion Factors and Assumptions -- None

I.A.2. Principal and Supporting Studies (Oral RfD)

Arnold, D.L., F. Bryce, R. Stapley et al. 1993a. Toxicological consequences of Aroclor 1254 ingestion by female Rhesus (Macaca mulatta) monkeys, Part 1A: Prebreeding phase - clinical health findings. Food Chem. Toxicol. 31: 799- 810.

Arnold, D.L., F. Bryce, K. Karpinski et al. 1993b. 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: 811-824.

Tryphonas, H., S. Hayward, L. O'Grady 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., M.I. Luster, G. Schiffman et al. 1991a. Effect of chronic exposure of PCB (Aroclor 1254) on specific and nonspecific immune parameters in the rhesus (Macaca mulatta) monkey. Fund. Appl. Toxicol. 16(4): 773-786.

Tryphonas, H., M.I. Luster, K.L. White et al. 1991b. Effects of PCB (Aroclor 1254) on non-specific immune parameters in Rhesus (Macaca mulatta) monkeys. Int. J. Immunopharmacol. 13: 639-648.

Groups of 16 adult female rhesus monkeys ingested gelatin capsules containing Aroclor 1254 (Monsanto Lot No. KA634) in 1:1 glycerol: corn oil vehicle daily at dosages of 0, 5, 20, 40 or 80 ug/kg-day for more than 5 years. The Aroclor mixture contained 5.19 ppm of polychlorinated dibenzofurans and undetectable levels of polychlorinated dibenzo-p-dioxins (Truelove et al., 1990). At study initiation the monkeys were 11.1 +/- 4.1 years old (Tryphonas et al., 1991a,b; Arnold et al., 1993a,b). After 25 months of exposure the monkeys had achieved a pharmacokinetic steady-state based on PCB concentrations in adipose tissue and/or blood (Tryphonas et al., 1989). Results of general health and clinical pathology evaluations conducted during the first 37 months of exposure were reported by Arnold et al. (1993a,b). Results of immunologic assessments after 23 and 55 months of exposure were reported by Tryphonas et al. (1989, 1991a,b). Results of reproductive endocrinology evaluations after 24 or 29 months of exposure were reported by Truelove et al. (1990) and Arnold et al. (1993a). Effects on hydrocortisone levels during the first 22 months of exposure were reported by Loo et al. (1989) and Arnold et al. (1993b). All of the aforementioned evaluations were performed during the prebreeding phase of the study. Results of reproduction and histopathology evaluations in these monkeys are not fully available (Arnold, 1992).

General health status was evaluated daily, and body weight measurements, feed conversion ratio calculations, and detailed clinical evaluations were performed weekly throughout the study. Analyses of clinical signs of toxicity were limited to the occurrence of eye exudate, inflammation and/or prominence of the eyelid Meibomian (tarsal) glands, and particular changes in finger and toe nails (prominent nail beds, separation from nail beds, elevated nail beds, and nails folding on themselves). Each endpoint was analyzed for individual treatment-control group differences and dose-related trends with respect to incidence rate, total frequency of observed occurrences, and the onset time of the condition. With respect to effects on the eyes, the treatment-control group comparisons showed statistically significant (p less than or equal to 0.05) increases in the total frequency of inflamed and/or prominent Meibomian glands at 0.005, 0.02 and 0.08 mg/kg-day, and decreased onset time for these effects at 0.08 mg/kg-day.

Significant dose-related trends (p less than or equal to 0.05) were observed for increased total frequencies of inflamed and/or prominent Meibomian glands, decreased onset time of inflamed and/or prominent Meibomian glands, and increased incidences of eye exudate. With respect to effects on finger and/or toe nails, the treatment-control group comparisons showed significantly (p less than or equal to 0.05) increased incidence of certain nail changes at 0.005 mg/kg-day (nail folding) and 0.08 mg/kg-day (elevated nails), increased total frequency of certain nail changes at 0.005 mg/kg-day (nail separation), 0.04 mg/kg-day (nail folding and separation) and 0.08 mg/kg-day (nail folding and separation, prominent beds, elevated nails), and decreased onset time of certain nail changes at 0.005 mg/kg-day (elevated nails) and 0.08 mg/kg-day (nail folding, prominent beds, elevated nails). Significant dose-related trends (p less than or equal to 0.05) were observed for certain nail changes (prominent beds, elevated nails) when adjusted for onset time, total frequencies of certain nail changes (nail folding and separation, prominent beds, elevated nails), and decreases in onset time of certain nail changes (nail folding, prominent beds, elevated nails).

Immunologic assessment showed significant ($p<0.01$ or <0.05) reductions in IgG (at all doses of Aroclor 1254) and IgM (all doses but 0.02 mg/kg-day) antibody levels in response to injected sheep red blood cells (SRBC) after 23 months of exposure (Tryphonas et al., 1989). A significant ($p<0.05$) decrease in the percent of helper T-lymphocytes, a significant ($p<0.05$) increase in the percent and absolute level of suppressor T-lymphocytes (TS) and a significant ($p<0.01$) reduction in TH/TS ratio was observed at 0.08 mg/kg-day. The antibody response to SRBC is an antigen-driven response that requires the interaction of several distinct cell types (i.e., antigen processing and presentation by macrophages, participation by T-helper cells and finally proliferation and differentiation of B cells into plasma cells that secrete the antibody), which result in the production and secretion of antibodies specific for SRBC from plasma cells. Perturbation in any of the cells or cell-to-cell interactions by physical, chemical or biological agents can result in aberrant antibody responses. The necessity for the interaction of the three principal cells of the immune system (i.e., macrophage, B lymphocyte and T lymphocyte), in response to SRBC, is the main reason why this response has been so widely used in immunotoxicity testing as a surrogate for infection with a pathogenic organism.

In a recent evaluation of the sensitivity and predictability of various immune function assays used for immunotoxicity testing in the mouse (Luster et al., 1992), the antibody plaque-forming cell (PFC) response to SRBC was found to show the highest association with immunotoxic compounds. Essentially this means that the antibody PFC response to SRBC is a very good predictor of immunotoxicants. Also, it has recently been demonstrated that measurement of serum antibody titer to SRBC using the ELISA assay is as sensitive as the PFC assay for determining the response to SRBC (Butterworth et al., 1993).

There were no exposure-related effects on total B-lymphocytes, total T- lymphocytes, total serum immunoglobulin levels, total serum protein, serum protein fractions after 23 months. No exposure-related effects on serum hydrocortisone levels were observed although the SRBC assay is considered a good surrogate (Tryphonas et al., 1989; Loo et al., 1989; Arnold et al., 1993b).

After 55 months of exposure, there was a significant dose-related decrease ($p<0.0005$ for pairwise comparisons and trend test) in the IgM antibody response to injected SRBC at greater than or equal to 0.005 mg/kg-day at all times of evaluation (1-4 weeks postimmunization) (Tryphonas et al., 1991a). IgG antibody response to injected SRBC was significantly ($p<0.01$) decreased only at 0.04 mg/kg-day, although the overall trend for dose-response was significant ($p=0.033$). The antibody response to pneumococcus antigen did not differ significantly among all test groups (including controls) at any time tested and showed no dose-related trend. However, the antibody response to pneumococcus antigen is a T cell-independent response and the fact that there is no change with this antigen is not inconsistent with the depressed response to the T cell-dependent SRBC antigen. Other data corroborate the significance of Aroclor 1254 suppression of the antibody response to SRBC and point to effects on T lymphocytes including the dose-related suppression of the Con A and PHA lymphoproliferative responses. The monkeys treated with greater than or equal to 0.005 mg/kg-day had significantly ($p<0.0001$) lower mean percentage levels of total T-lymphocytes and significant trend for dose-response, but absolute numbers of T-lymphocytes were similar among test groups. Flow cytometric analysis showed no treatment-related effects on peripheral blood T- helper, T-suppressor or B-lymphocytes or TH/TS lymphocyte ratio. A statistically significant, dose-related increase was noted for thymosin alpha-1-levels but not for thymosin beta-2-levels. Serum complement activity was significantly ($p<0.025$) increased at greater than or equal to 0.005 mg/kg-day but showed no significant ($p=0.1$) dose-related trend. Natural killer cell activity at effect or target ratios of 25:1, 50:1 or 75:1 was not significantly ($p>0.05$) increased at any dosage, although there was a significant ($p=0.03$) dose-related trend. No signs of microbial infection were noted in any of the preceding reports.

Clinical pathology was evaluated during the first 37 months of the study (Arnold et al., 1993b). These evaluations included monthly measurements of hematology and serum biochemistry (including serum protein, RBC indices, semi- monthly measurements of thyroid function, and daily measurements of urinary porphyrins during the 33rd month of dosing). Significant (pó0.05) decreases in average dose-group values compared with controls were found for serum cholesterol at 0.04 mg/kg-day, and reticulocyte count, serum cholesterol, total bilirubin, and alpha-1 + alpha-2-globulins at 0.08 mg/kg-day. Significant dose-related decreasing linear trends were also observed for reticulocyte count ($p=0.002$), cholesterol (p less than or equal to 0.001), and total bilirubin ($p=0.005$). Dose-related decreasing linear trends were also observed for red blood cell count ($p=0.019$), mean platelet volume ($p=0.034$), hematocrit ($p=0.064$), hemoglobin concentration ($p=0.041$). With regard to thyroid endpoints [serum thyroxine (T4), serum

triiodothyronine (T3) uptake ratio, percent T3 uptake, and free thyroxine index], dose-response analysis consisted of group mean comparisons and an assessment of parallelism in the response profiles (an absence of parallelism would indicate time-dose interactive effects). No statistically significant changes were observed for any of the thyroid endpoints.

After approximately 2 years of dosing, each dose group was randomly divided into two test groups for daily analyses of serum progesterone and estrogen concentrations during one menstrual cycle (Truelove et al., 1990; Arnold et al., 1993b). There were no statistically significant differences between treated and control monkeys in menstrual cycle length or menses duration, and no apparent treatment-related effects on incidence of anovulatory cycles or temporal relationship between estrogen peak and menses onset, menses end or progesterone peak (Truelove et al., 1990; Arnold et al., 1993a,b).

To summarize the above, monkeys that ingested 0.005-0.08 mg/kg-day doses of Aroclor 1254 showed ocular exudate, prominence and inflammation of the Meibomian glands and distortion in nail bed formation. These changes were seen at the lowest dose tested, 0.005 mg/kg-day, and a dose-dependent response was demonstrated. Similar changes have been documented in humans for accidental oral ingestion of PCBs. Among the various immunologic function tests that were performed, the increases in IgM and IgG antibodies to sheep erythrocytes are most significant. IgG and IgM antibodies in response to SRBC were reduced after 23 months of exposure but only the IgM antibodies were clearly decreased after 55 months. Particular importance is attributed to the immune response to sheep erythrocytes since it involves participation by the three principal cells of the immune system: the macrophage, B lymphocytes and T lymphocytes and has been shown to be the most predictive immunotoxicity test of those currently in use (Luster et al., 1992). On the basis the studies described, a LOAEL of 0.005 mg/kg-day was established for Aroclor 1254.

I.A.3. Uncertainty and Modifying Factors (Oral RfD)

UF — A 10-fold factor is applied to account for sensitive individuals. A factor of 3 is applied to extrapolation from rhesus monkeys to humans. A full 10-fold factor for interspecies extrapolation is not considered necessary because of similarities in toxic responses and metabolism of PCBs between monkeys and humans and the general physiologic similarity between these species. A partial factor is applied for the use of a minimal LOAEL since the changes in the periocular tissues and nail bed see at the 0.05 mg/kg-day are not considered to be of marked severity. The duration of the critical study continued for approximately 25% of the lifespan of rhesus monkeys so that a reduced factor was used for extrapolation from subchronic exposure to a chronic RfD. The immunologic and clinical changes that were observed did not appear to be dependent upon duration which further justifies using a factor of 3 rather than 10 for extrapolation from subchronic to chronic, lifetime exposure. The total UF is 300.

MF — None

I.A.4. Additional Studies/Comments (Oral RfD)

Human data available for risk assessment of Aroclor 1254 are useful only in a qualitative manner. Studies of the general population who were exposed to PCBs by consumption of contaminated food, particularly neurobehavioral evaluations of infants exposed in utero and/or through lactation, have been reported, but the original PCB mixtures, exposure levels and other details of exposure are not known (Kreiss et al., 1981; Humphrey, 1983; Fein et al., 1984a,b; Jacobson et al., 1984a, 1985, 1990a,b; Rogan et al., 1986; Gladen et al., 1988). Most of the information on health effects of PCB mixtures in humans is available from studies of occupational exposure. Some of these studies examined workers who had some occupational exposure to Aroclor 1254, but sequential or concurrent exposure to other Aroclor mixtures nearly always occurred, exposure involved dermal as well as inhalation routes (relative contribution by each route not known), and monitoring data are lacking or inadequate (Alvares et al., 1977; Brown and Jones, 1981; Colombi et al., 1982; Fischbein et al., 1979, 1982, 1985; Fischbein, 1985; Warshaw et al., 1979; Smith et al., 1982; Taylor et al., 1984; Lawton et al., 1985). Insufficient data are available in these studies to determine possible contributions of Aroclor 1254 alone, extent of direct skin exposure and possible contaminants. However, it is relevant to note that dermal and ocular effects, including skin irritation, chloracne, hyperpigmentation and eyelid and conjunctival irritation, have been observed in humans occupationally exposed to Aroclor 1254 and other Aroclor formulations.

Aroclor 1254 was fed to groups of eight female and four male adult rhesus monkeys once daily in dosages of 0, 5, 25 or 100 ug/kg for 14 months, followed by an observation period of 7 months (Levinskas et al., 1984). The Aroclor 1254 was dissolved in corn oil and offered to the animals in apple sauce prior to each day's feeding, and the control mixture (corn oil in applesauce) was used during the observation period. Dosages were adjusted biweekly for changing body weight as necessary. The monkeys were selected on the basis of a successful reproductive history, estimated to be at least 6 years old, and had been in captivity for 2-9 years. After 6 months of treatment the monkeys were bred to untreated males or females from the same colony over an 8-month period and offspring were observed for 2 months. Breeding was continued until conception was diagnosed by digital examination of the uterus and alterations in the menstrual cycle. Evaluations of adult animals included hematology and clinical chemistry. Urinalysis was also performed every 3 months during the study. Semen analyses were performed monthly from just prior to the start of treatment until the end of the treatment period. After 2 months of observation; sperm concentration, total sperm, sperm motility, percent abnormal cells and live/dead ratios were evaluated. Based upon these parameters, no effect was observed upon male reproductive capacity. Necropsies including histological examinations were performed on all adult animals that died during the study or were euthanized at the end of the observation period.

Birth weight and somatic measurements were taken for all offspring of exposed females or males. The infants of the exposed females were subsequently evaluated monthly for body weight and complete blood cell counts were performed. Infants that did not show signs of intoxication were euthanized after 2 months and those showing signs were weaned, observed for reversal of signs, and euthanized at the end of the study along with the adults. Necropsies including histological examinations were performed on all infants that died or were euthanized.

Death or euthanasia in extremis occurred in 1/12, 0/12, 1/12 and 5/12 of the adult monkeys in the control, low-, mid- and high-dose groups, respectively. All of the deaths occurred in females except for one male in the high-dose group, and the only deaths considered to be related to treatment were in four of the high-dose animals (3 females, 1 male). Characteristic signs of PCB intoxication developed in the high-dose group after 9 months of exposure, including effects on the eyelids (redness and/or edema, wrinkling) in approximately half the animals and swelling of the lips in all animals. Other characteristic signs included bleeding gums, abnormal fingernail/toenail growth pattern and increased alopecia (including eyelashes) in several of the high-dose monkeys. In general, the signs of intoxication appeared to subside during the post-treatment period. Some of the monkeys in the mid-dose group showed signs of intoxication (swelling of the lips in one male and one female) after 15 and 18 months, respectively, and alopecia and abnormal nail growth, but no signs attributable to exposure occurred in the low-dose group. Hematologic effects at the high dose were observed including reduced packed cell volume, erythrocyte count, hemoglobin and platelet counts. In addition, increased serum iron and reduced serum cholesterol were observed, particularly in the monkeys that died. Some of the high-dose monkeys also had prolonged bleeding and improper healing at biopsy sites. Dermal histological changes characteristic of PCB poisoning were prominent in the high-dose group, occurring in 11/12 monkeys (8 females, 3 males), and included loss of secretory epithelium in the Meibomian (eyelid) glands and sebaceous glands, partial or total atrophy of sebaceous glands, follicular keratosis and/or squamous cysts. Dermal changes also occurred in four of the mid-dose monkeys, but not in the low-dose or control groups. Other histological alterations included squamous metaplasia in glandular ducts of the tongue or lip (3 high- dose females, 1 high-dose male), subgingival epithelial cysts of the mandible (1 high-dose male, 1 high-dose female, 1 mid-dose male) and hyperplasia in the bile and pancreatic ducts and gall bladder (1 high-dose female). Nonspecific bone marrow alterations (decreased cellularity and/or granulocyte maturation) occurred in 6/12 high-dose monkeys (5 females, 1 male) and may have been compound-related because they correlated with the hematologic changes.

There was no apparent effect on male fertility based on conception rate following matings with the untreated females or the semen analyses (Levinskas et al., 1984). In the female control, low-, mid- and high-dose groups, the numbers of known pregnancies were 7, 7, 7 and 5, respectively, the numbers of live births were 6, 5, 7 and 1, respectively. Analysis of the preceding data showed that there was a statistically significant reduction in fertility in the high-dose group; this analysis

refers only to the decreased number of live births. There was a clear exposure-related effect on birth weight and infant body weight gain. When compared with control group infants (mean birth weight 495.2 g) the 0.025 mg/kg-day infants (mean birth weight 392.2 g) showed a statistically significant reduction in birth weight ($p<0.005$). Most of the infants in the mid-dose group and all of the infants in the high-dose had abnormal clinical signs. These changes included being born with or developed dermal signs that were consistent with those in the adults (e.g., swollen lips, swollen eyelids and/or scanty eyelashes) and more severe at the high dose, and also developed pulmonary signs (e.g., respiratory wheezing). Histological changes in the infants were generally similar to those observed in the adults. These effects included changes in the Meibomian and sebaceous glands, pancreatic ducts and bone marrow. Other histological changes included thymic atrophy in one mid-dose and the high-dose infant, and other effects in the high-dose infant (e.g., retarded kidney cortical maturation, bile duct hyperplasia and gastric mucosal gland cysts).

To summarize the above, no treatment-related effects were observed in the low-dose adults or their infants, indicating that 0.005 mg/kg-day is a NOAEL. For the mid-dose infants there was a 15% reduction in birth weight of infants that was statistically significant ($p<0.005$). When these infants reached 2 months of age the reduced body weight was 22% below controls and this difference was also found to be statistically significant ($p=0.05$). Ocular and dermal signs and/or histological changes characteristic of PCB intoxication developed in some adults receiving 25 and 100 ug/kg-day, as well as in most of the infants in these groups. Based on these effects the 0.025 mg/kg-day dosage is a LOAEL. Other effects at the high dose included decreased adult survival, female fertility and numbers of live births, indicating that 0.1 mg/kg-day is a FEL. This FEL is supported by results of the Truelove study (Truelove et al., 1982).

Aroclor 1254 was fed to 1, 2 or 1 pregnant rhesus monkeys in reported average daily doses of 0, 0.1 or 0.2 mg/kg-day, respectively, 3 days/week for up to 267 days starting on gestation day 60 (Truelove et al., 1982). The exposure period included gestation and lactation. One of the adult monkeys in the low-dose group and the one adult in the high-dose group lost their fingernails after 233 and 242 days of PCB treatment, but other overt signs of intoxication were not observed. There was a significant reduction in antibody production in response to injected SRBC in the exposed monkeys, but levels of antibody production to tetanus toxoid were not appreciably different from control. The two low-dosage monkeys delivered dead infants. The infant of the high-dosage monkey died at age 139 days; this infant showed impaired immune function as assessed by antibody production following SRBC injections. Hematological evaluation performed bimonthly following parturition in adults and the surviving infant were inconclusive. Although evaluation of the dead infants and other results of this study is complicated by the small number of animals, the characteristic dermal sign of PCB toxicity in the exposed monkeys and lack of effects in controls strongly indicate that the developmental toxicity is exposure-related. Therefore, based on the stillbirths, 0.1 mg/kg- day is a FEL in monkeys.

Groups of four young adult female rhesus monkeys were fed 0 or 0.28 mg/kg doses of Aroclor 1254 for 5 days/week for 114-121 weeks (Tryphonas et al., 1986a,b; Arnold et al., 1990). Groups of four mature adult female cynomolgus monkeys that had a poor breeding history were similarly exposed for 55-58 weeks (Tryphonas et al., 1986a; Arnold et al., 1990). The Aroclor mixture contained no detectable polychlorinated dibenzo-p-dioxin contaminants. Adjusting for the partial weekly exposure gives an average daily dosage of 0.2 mg/kg-day. Prominent clinical signs appeared in all exposed rhesus monkeys during the first 2-12 months of exposure, including facial and periorbital edema, loss of eyelashes, Meibomian gland enlargement and impaction, conjunctivitis, nail lesions progressing from dryness to detachment and gingival hyperplasia and necrosis of varying severity. Two of the exposed rhesus monkeys developed overwhelming infections of the eye or periodontal tissue after 27 months of exposure prompting sacrifice within 48 hours. The hematology and serum biochemistry evaluations showed various changes in the exposed rhesus monkeys, particularly slight or moderate normocytic anemia, depressed erythropoiesis in bone marrow and increased triglycerides and SGOT. The immunologic testing was inconclusive due to large interspecies variability. Pathology findings in the exposed rhesus monkeys included effects in the liver of three monkeys (30-55% increased relative liver weight, hepatocellular hypertrophy and necrosis, bile duct epithelial hypertrophy and hyperplasia, gall bladder epithelial hypertrophy), thyroid of two monkeys (enlargement, occasional follicular cell desquamation) and stomach of two monkeys (hypertrophic gastropathy). The cynomolgus monkeys had effects that were generally consistent with but less extensive and severe than those observed in the rhesus monkeys. After 38 weeks of exposure the rhesus monkeys were mated with untreated males; cynomolgus monkeys were not mated. The control and exposed rhesus monkeys became pregnant within 7 and 8 matings, respectively. Following extended post-implant bleeding all of the treated rhesus monkeys aborted within 30-60 days of gestation. Following recovery from the abortions the monkeys were bred again up to a maximum of seven times but none appeared to conceive. The menstrual cycle lengths and durations became erratic and longer during and subsequent to the breeding. Based on the abortions, reproductive impairment and pronounced overt signs of toxicity, the 0.2 mg/kg-day dosage is an FEL in monkeys.

Aulerich and Ringer (1977) performed a breeding study in which groups of eight female and two male adult mink were fed diets containing 0 or 2 ppm Aroclor 1254 for 39 weeks or until the kits were 4 weeks of age. The Aroclor was dissolved in acetone which was evaporated from the diet prior to feeding. Using assumed values of 150 g/day for food consumption and 0.8 kg for body weight for female mink (Bleavins et al., 1980), the estimated dosage of Aroclor 1254 is 0.4 mg/kg-day. Approximately monthly determinations reportedly showed no statistically significant ($p<0.05$) differences between the control and treated mink in body weight gain, hemoglobin, and hematocrit. Only two of seven mated females gave birth, producing one infant each. Of the two infants, one was born dead and the other had low body weight and was dead by age 4 weeks.

Based on the reproductive and/or fetal toxicity resulting in nearly complete lack of births, 0.4 mg/kg-day is a FEL for Aroclor 1254 in mink.

Twelve female and four male adult ranch-bred mink (age 8 months, body weight not reported) were fed a diet containing 1 ppm Aroclor 1254 for 6 months (Wren et al., 1987a,b). Groups of 15 females and five males were used for unexposed controls. The mink were bred after approximately 12-14 weeks of exposure and exposure was continued until weaning at age 5 weeks. Using assumed values for food consumption and for body weight for female mink (Bleavins et al., 1980), the estimated dosage of Aroclor 1254 is 0.15 mg/kg- day. Offspring mortality during the first week of life was 75.8% higher in the exposed group than in the controls. Average body weight was significantly lower in the exposed offspring at age 3 and 5 weeks, but not at age 1 week, suggesting that transfer of PCBs by lactation may have contributed to the effect. There were no exposure-related effects on adult survival or mating performance, number of offspring per female mated or female that delivered, adult thyroid plasma T3 or T4 levels during the exposure period, adult scrotal diameter, offspring survival or relative liver weight at weaning or organ weights or histology (brain, kidney, adrenal, pituitary, thyroid). Teratogenicity was not evaluated. The neonatal mortality indicates that 0.15 mg/kg-day is an FEL in mink.

Groups of 10 female Sprague-Dawley rats were fed 0, 1, 5, 10 or 50 ppm Aroclor 1254 in the diet for approximately 5-6 months (Byrne et al., 1987). The Aroclor was dissolved in acetone which was evaporated from the diet prior to feeding. Based on reported body weight and food consumption data the dosages are estimated to be 0.09, 0.43, 0.61 and 4.3 mg/kg-day. Serum thyroxine (T4) and triiodothyronine (T3) were evaluated at five different times during 140 and 175 days of treatment, respectively. Serum T4 levels were significantly reduced at 0.09 and 0.43 mg/kg-day by day 35 and at greater than or equal to 0.61 mg/kg-day by day 14. T3 levels were significantly reduced at 0.09 mg/kg-day by day 40 and at greater than or equal to 0.4 mg/kg- day by day 20. The suppressions were generally dose-related for T4 throughout the treatment period and T3 after 75 days. Disappearance rate of injected L- [125I] T4 was significantly decreased at greater than or equal to 0.09 mg/kg- day. Rats treated with only 0.43 or 0.61 mg/kg-day for approximately 5 months and challenged with i.p. injected TSH had diminished response of serum T4 and T3. Thyroid histology was not evaluated. There were no treatment-related effects on relative thyroid weight, body weight or food consumption. The findings of this study indicate that the decreased serum T3 and T4 resulted primarily from direct damage to the thyroid rather than suppression of the hypothalamo-pituitary axis or any enhanced peripheral catabolism (e.g., liver). Insufficient data are available to determine if the decreases in circulating thyroid hormones were physiologically significant. However, because the effects are indicative of impaired organ function, they are at least potentially adverse and 0.09 mg/kg-day is considered to represent a LOAEL in rats.

Groups of 10 female Sprague-Dawley rats were fed 0, 1, 5, 10 or 50 ppm Aroclor 1254 in the diet for 5 months (Byrne et al., 1988). The Aroclor was dissolved in acetone which was evaporated from the diet prior to feeding. Using a rat food consumption factor of 0.05 kg food/kg body weight, the dosages are estimated to be 0.05, 0.25, 0.5 and 2.5 mg/kg-day. Serum levels of adrenal cortex hormones were evaluated in 8-10 rats 3-5 times during the treatment period. Serum corticosterone was significantly ($p<0.05$) decreased at greater than or equal to 0.25 mg/kg-day after approximately 60 days of exposure. Serum dehydroepiandrosterone and dehydroepiandrosterone sulfate were significantly ($p<0.05$) decreased at 0.25 and 0.5 mg/kg-day (not evaluated at other dosages) after approximately 100 days and 25 days of exposure, respectively. Serum corticosterone is the principal glucocorticoid in rats. Adrenal weight, adrenal histology and non-adrenal endpoints other than food consumption were not evaluated. Food consumption did not significantly differ between and among control and treatment groups. The results of this study are suggestive of toxicity to the adrenal rather than response to stress which would be expected to increase the release of glucocorticoids. Insufficient data are available to determine if the decreases in circulating adrenal cortex hormones were physiologically significant. However, because the effects are indicative of impaired organ function, they are at least potentially adverse. The dosages of 0.05 and 0.25 mg/kg-day therefore are considered to represent a NOEL and LOAEL, respectively, in rats.

Hepatotoxicity is a prominent effect of Aroclor 1254 that is well characterized in rats (U.S. EPA, 1990). The spectrum of effects includes hepatic microsomal enzyme induction, increased serum levels of liver- associated enzymes indicative of possible hepatocellular damage, liver enlargement, lipid deposition, fibrosis and necrosis. Estimated subchronic dosages as low as 1.25-2.5 mg/kg-day have been reported to produce increased liver weight and hepatic biochemical alterations in rats, but the lowest dosages producing signs of hepatic effects are generally higher than the lowest dosages that caused thyroid, adrenal and bone changes (Litterset et al., 1972; Bruckner et al., 1974; Kling and Gamble, 1982; Andrews et al., 1989). Rats fed 6.8 mg/kg-day for 8 months (Kimbrough et al., 1972) or an estimated dosage of 50 mg/kg-day for 30 days (Kling et al., 1978) developed fatty and necrotic degenerative hepatic histologic changes. Chronic dietary exposure to 1.25-5 mg/kg-day for approximately 2 years produced only preneoplastic and neoplastic liver lesions in rats (NCI, 1978; Ward, 1985).

A two-generation reproduction study was performed in which groups of 20 female and 10 male Sherman rats (age 3-4 weeks, body weight not reported) were fed 0, 1, 5, 20 or 100 ppm dietary Aroclor 1254 (Monsanto Lot No. AK-38) in peanut oil vehicle (Linder et al., 1974). Reported dosages were 0.06, 0.32, 1.5 and 7.6 mg/kg-day, and different controls were used for the less than or equal to 0.32 and greater than or equal to 1.5 mg/kg-day groups. Exposure times (before mating or conception-to-mating) ranged from 62-274 days. Exposure-related effects included increased relative liver weight in F1a weanlings at greater than or equal to 0.06 mg/kg-day, enlarged and vacuolated hepatocytes in F2a weanlings at greater than or equal to 1.5 mg/kg-day,

and 15-72% reduced litter size at greater than or equal to 1.5 mg/kg-day in the F1b, F2a and F2b generations and at 7.6 mg/kg-day in the F1a generation. Relative testes weights were increased in adult F1b males at 7.6 mg/kg-day (other groups not evaluated). The highest NOAEL is 0.32 mg/kg-day based on the increased liver weight without altered histology. The decreased litter size indicates that 1.5 mg/kg-day is a FEL.

A one-generation reproduction study was performed in which groups of 10 male and 10 female Sherman rats were fed 0, 100 or 500 ppm dietary Aroclor 1254 for 67 or 186 days prior to pair-mating for the F1a and F1b generations, respectively (Linder et al., 1974). The F0 rats received reported dosages of 0, 7.2 and 37.0 mg/kg-day and were sacrificed after a total exposure duration of 8 months for hematology, organ weight and liver histology evaluation. The study was terminated after the F1b pups were weaned. Effects in the P1 rats included increased liver weight in both sexes greater than or equal to 7.2 mg/kg-day, increased relative testis weight (absolute weight unchanged) at 37.0 mg/kg-day, decreased body weight gain in both sexes at 37.0 mg/kg-day, and changes in hematological values (reduced hematocrit and hemoglobin in both sexes, increased total leukocytes with normal differential count in females) at 37.0 mg/kg-day. Specific information on liver pathology was not reported but degenerative changes similar to those found in the Kimbrough et al. (1972) subchronic study were indicated for both dosages. Effects on the offspring included reduced survival to weaning at 7.2 mg/kg-day (85.9 and 68.1% survival in F1a and F1b pups, respectively, compared with 95.5% in controls), and reduced litter size and number and 100% pup mortality by day 3 in F1a rats at 37.0 mg/kg-day. The decreases in postnatal survival indicate that both dosages are FELs.

Groups of six to eleven female Wistar rats were fed 2.5, 26 or 269 ppm Aroclor 1254 in the diet during gestation and lactation (Overman et al., 1987). A control group was fed untreated diet that contained 0.02 ppm PCBs (i.e., no added PCBs). Using a rat food consumption factor of 0.05 kg food/kg body weight, the dosages are estimated to be 0.001, 0.13, 1.3 and 13.5 mg/kg- day. The following neurobehavioral endpoints were significantly delayed or reduced in the pups: appearance of the auditory startle response at 0.13 and 1.3 mg/kg-day at age 6 days (slightly delayed), development of righting ability at 1.3 mg/kg-day at days of age (slightly delayed) and performance on a motor coordination test at 1.3 mg/kg-day at age 7 and 8 days (slower performance). Grip strength and appearance of eye opening were not affected by exposure. Other effects attributable to exposure included increased relative liver weight in pups at weaning at greater than or equal to 1.3 mg/kg-day and reduced birth weight, 50% mortality by 2 days of age and retarded growth in pups at 13.5 mg/kg-day. There were no exposure-related effects on maternal weight gain, gestation length, litter size, pup sex ratios, number of live and dead pups or physical appearance, relative spleen and thymus weight or relative and absolute brain weight of pups. Brain PCB levels increased from birth to weaning in all groups. Based on the evidence for impaired motor coordination in developing infants the 0.13 and 1.3 mg/kg- day dosages are a NOAEL and LOAEL, respectively.

Dietary Aroclor 1254 was administered to groups of 4-10 female ICR mice in concentrations of 0, 1, 10 or 100 ppm from 90 days before mating through gestation day 18 (Welsch, 1985). The investigators estimated the dosages to be 0.125, 1.25 and 12.5 mg/kg-day. No developmental toxicity was observed as judged by number of litters, number of dead and reabsorbed fetuses, fetal weight, incidence of gross malformations or skeletal development. Fetuses were not examined for internal malformations. Maternal effects other than significantly increased relative liver weight at greater than or equal to 0.125 mg/kg-day were not observed. No developmental effects were observed in mice treated with the same doses of PCB only on gestation days 6-18. Based on the increased maternal liver weight the highest NOAEL is 12.5 mg/kg-day.

Groups of seven adult male New Zealand white rabbits were fed dietary Aroclor 1254 in reported estimated dosages of 0, 0.18, 0.92, 2.10 or 6.54 mg/kg-day for 8 weeks (Street and Sharma, 1975). Immunological testing was started after 4 weeks of treatment at which time the rabbits were immunized with injected SRBCs. No treatment-related changes in serum antibody titers to SRBC (hemolysin and hemagglutination) were observed. SRBC-induced increases in serum gamma-globulin were consistently but not statistically significantly decreased by exposure, and the number of globulin-producing cells in popliteal lymph nodes was significantly decreased at 0.92 and 6.54 mg/kg-day. Skin sensitivity to tuberculin was generally lower in the treated groups but none of the decreases were statistically significant. Marked histologic atrophy of the thymus cortex was observed at 0.18 mg/kg-day and higher dosages except 0.92 mg/kg-day. There were no treatment-related effects on leukocyte count, histology of the spleen, thymus, liver, kidneys or spleen, relative kidney or adrenal weight, terminal body weight or food consumption. Relative liver and spleen weights were significantly increased at greater than or equal to 2.10 mg/kg-day; the increase in liver weight was 74% at the highest dosage. The 0.18 mg/kg-day dosage is a LOAEL based on the thymic cortical atrophy.

Limited specific information is available on the oral absorption of Aroclor 1254. Pregnant ferrets that ingested a single oral dose of Aroclor 1254 (approximately 0.06 mg/kg) absorbed approximately 85% of the initial amount (Bleavins et al., 1984). Studies predominately of individual chlorobiphenyl congeners indicate, in general, that PCBs are readily and extensively absorbed by animals. These studies have found oral absorption efficiency on the order of 75 to >90% in rats, mice and monkeys (Albro and Fishbein, 1972; Allen et al., 1974; Tanabe et al., 1981; Clevenger et al., 1989). A study of a non-Aroclor 54% chlorine PCB mixture prepared by the investigators provides direct evidence of absorption of PCBs in humans after oral exposure (Buhler et al., 1988), and indirect evidence of oral absorption of PCBs by humans is available from studies of ingestion of contaminated fish by the general population (Schwartz et al., 1983; Kuwabara et al., 1979). There are no quantitative data regarding inhalation absorption of PCBs in humans but studies of workers exposed suggest that PCBs are well absorbed by the inhalation and dermal routes (Maroni et al., 1981a,b; Smith et al., 1982; Wolff, 1985). PCBs distribute

preferentially to adipose tissue and concentrate in human breast milk due to its high fat content (Jacobson et al., 1984b; Ando et al., 1985).

The metabolism of PCBs following oral and parenteral administration in animals has been extensively studied and reviewed, but studies in animals following inhalation or dermal exposure are lacking (Sundstrom and Hutzinger, 1976; Safe, 1980; Sipes and Schnellmann, 1987). Information on metabolism of PCBs in humans is limited to occupationally exposed individuals whose intake is derived mainly from inhalation and dermal exposure (Jensen and Sundstrom, 1974; Wolff et al., 1982; Schnellmann et al., 1983; Safe et al., 1985; Fait et al., 1989). In general, metabolism of PCBs depends on the number and position of the chlorine atoms on the phenyl ring of the constituent congeners (i.e., congener profile of the PCB mixture) and animal species. Although only limited data are available on metabolism of PCBs following inhalation exposure, there is no reason to suspect that PCBs are metabolized differently by this route.

Data exist on the in vitro hepatic metabolism and in vivo metabolic clearance of 2,2',3,3',6,6'-hexachlorobiphenyl and 4,4'-dichlorobiphenyl congeners in humans, monkeys, dogs and rats (Schnellmann et al., 1985). The hexachlorobiphenyl congener is a constituent of Aroclor 1254. For each congener, the Vmax values for metabolism in the monkey, dog and rat are consistent with the respective metabolic clearance values found in vivo. Thus, the kinetic constants for PCB metabolism obtained from the dog, monkey and rat hepatic microsomal preparations were good predictors of in vivo metabolism and clearance for these congeners. In investigations directed at determining which species most accurately predicts the metabolism and disposition of PCBs in humans, the in vitro metabolism of these congeners was also studied using human liver microsomes (Schnellmann et al., 1983, 1984). Available data suggest that metabolism of PCBs in humans would most closely resemble that of the monkey and rat. For example, the in vitro apparent Km and Vmax are comparable between humans and monkeys. These studies show consistency between the in vitro and in vivo findings and collectively indicate that metabolism of the two congeners is similar in monkeys and humans.

I.A.5. Confidence in the Oral RfD

Study — Medium
Database — Medium
RfD — Medium

Confidence in the principal study is medium. Groups of 16 rhesus monkeys were tested at four dose levels and LOAEL was established on the basis of clinical signs and immunologic alterations. Data for female and male reproductive function and developmental data in a nonhuman primate species is taken from an unpublished study (Levinskas et al., 1984) which established a NOAEL for reproductive effects at 0.005 mg/kg-day. The Arnold study also

included evaluation of reproductive function but the data have not been completely analyzed. Preliminary examination of the Arnold et al. data indicate that the LOAEL for female reproductive function may be 0.005 mg/kg- day. This inconsistency in effect levels for reproductive toxicity was viewed as a limitation to the database. Furthermore, there is a limitation in the characterization of reproductive toxicology because results of an unpublished study have been considered. An extensive number of laboratory animal and human studies were available for review, including two-generation reproductive studies. The chronic, 2-year bioassays performed in F344 rats showed evidence of degenerative hepatocellular changes in addition to the neoplastic changes that were observed. Only limited assessment of nonhepatic changes were made. Human occupational and environmental data is available for commercial PCB mixtures in general but not specifically for Aroclor 1254. The database is rated medium on the basis of these considerations. Overall confidence in the RfD is medium.

I.A.6. EPA Documentation and Review of the Oral RfD

Source Document — This assessment is not presented in any existing U.S. EPA document.

Other EPA Documentation — U.S. EPA, 1984, 1989, 1990

Agency Work Group Review — 06/16/1993, 02/16/1994

Verification Date — 02/16/1994

I.A.7. EPA Contacts (Oral RfD)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Aroclor 1254
CASRN — 11097-69-1
Primary Synonym — PCBs, Polychlorinated Biphenyls

Not available at this time.

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Aroclor 1254
CASRN — 11097-69-1
Primary Synonym — PCBs, Polychlorinated Biphenyls

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Aroclor 1254
CASRN — 11097-69-1
Primary Synonym — PCBs, Polychlorinated Biphenyls

VI.A. Oral RfD References

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VI.B. Inhalation RfC References

None

VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Aroclor 1254
CASRN — 11097-69-1
Primary Synonym — PCBs, Polychlorinated Biphenyls

Date	Section	Description
10/01/1994	I.A.	Oral RfD summary on-line

VIII. Synonyms

Substance Name — Aroclor 1254
CASRN — 11097-69-1
Primary Synonym — PCBs, Polychlorinated Biphenyls
Last Revised — 07/01/1993

- 11097-69-1
- Aroclor 1254
- Arochlor 1254
- CHLORIERTE BIPHENYLE, CHLORGEHALT 54% [German]
- CLORODIFENILI, CLORO 54% [Italian]
- DIPHENYLE CHLORE, 54% DE CHLORE [French]
- HSDB 6357
- NCI-C02664