2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209); CASRN 1163-19-5

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 2,2',3,3',4,4',5,5',6,6'-DECABROMODIPHENYL ETHER (BDE-209) CASRN 1163-19-5

File First On-Line 01/31/1987

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	yes	06/30/2008
Inhalation RfC (I.B.)	qualitative discussion	06/30/2008
Carcinogenicity Assessment (II.)	yes	06/30/2008

I. HEALTH HAZARD ASSESSMENTS FOR NONCARCINOGENIC EFFECTS

An IRIS health assessment of decabromodiphenyl ether (decaBDE) was previously entered on IRIS on 1/31/1987. An RfD of 0.01 mg/kg-day was derived based on a no-observed-adverse-effect level (NOAEL) of 1.0 mg/kg-day, the highest dose tested, identified in a 2-year study in rats (Kociba et al., 1975) and applying a UF of 100 for intra- and interspecies variability. Confidence in the RfD was considered low. The decaBDE formulation used in the Kociba et al. (1975) study contained 77% decaBDE, while the current commercial product typically consists of ≥97% BDE-209.

I.A. REFERENCE DOSE (RfD) FOR ORAL EXPOSURE

Substance Name — 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)
CASRN — 1163-19-5
Section I.A. Last Revised — 06/30/2008

The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily oral exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfD is intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action. It is expressed in units of mg/kg-day. Please refer to the guidance documents at http://www.epa.gov/iris/backgrd.html for an elaboration of these concepts. Because RfDs can be derived for the noncarcinogenic health effects of substances that are also carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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	Point of Departure	UF	RfD
Neurobehavioral effects	NOAEL: 2.22 mg/kg	300	0.007 mg/kg-day
Single dose gavage study in mice	LOAEL: 20.1 mg/kg		
Viberg et al. (2003)			

I.A.2. PRINCIPAL AND SUPPORTING STUDIES

TThe effect of BDE-209 on spontaneous motor behavior of NMRI male mice was investigated in adult animals exposed as neonates to a single oral dose of BDE-209 (Viberg et al., 2003). Male mice were given on postnatal day (PND) 3 or 19 single doses of 0, 2.22, or 20.1 mg/kg body weight BDE-209 (>99% purity) in a fat emulsion. Ten-day-old mice received 0, 1.34, 13.4, or 20.1 mg/kg. The spontaneous behavior test (measuring locomotion, rearing, and total activity) was conducted in 10 male mice randomly selected from three to five litters in each treatment group at 2, 4, and 6 months of age. The behavior variables were measured for a 60

minute period, divided into three consecutive 20 minute periods. In order to study time-dependent changes in habituation, an habituation ratio was calculated by dividing the motor behavior measures from the 40-60 minute observation period by those from the 0-20 minute period and multiplying by 100 for each of the three different variables: locomotion, rearing, and total activity. The habituation ratios from 2-, 4-, and 6-month-old male mice within each treatment group were then compared.

Treatment with BDE-209 caused no clinical signs of toxicity at any time during the experimental period. Control mice treated on PND 3, 10, or 19 exhibited normal habituation profiles. Pair-wise testing among adult mice exposed to 20.1 mg/kg on PND 3 and control groups indicated significant changes in all three spontaneous behavior variables at 2, 4, and 6 months of age. For the first 20 minutes, mice receiving 20.1 mg/kg displayed significantly less activity for locomotion, rearing, and total activity compared with controls. During the third 20 minute period, exposure of mice to 20.1 mg/kg on PND 3 caused significantly more activity for locomotion, rearing, and total activity than in controls at 2, 4, and 6 months. The only effect noted in mice exposed to 2.22 mg/kg was a significant decrease in total activity in the first 20 minute test period compared with the controls at 2 months of age. However, total activity returned to control level during the third 20-minute period. The lower dose of 2.22 mg/kg did not elicit any significant differences in these three variables compared with controls at 4 months of age. Lower activity was observed at 2.22 mg/kg during the first 20-minute period for the rearing variable at 6 months of age compared with controls, again returning to control level during the third 20-minute period. Mice exposed neonatally up to 20.1 mg/kg on either PND 10 or 19 did not show any significant differences in any of the variables after 2, 4, or 6 months, compared with controls. The authors indicated that the absence of effects on spontaneous activity in mice treated on PNDs 10 and 19 suggests that there is a critical window for the induction of the observed behavioral disturbances.

The habituation ratio calculated from the three spontaneous motor behavior variables (locomotion, rearing, and total activity) significantly increased after 2, 4, and 6 months of age in mice exposed on PND 3 to 20.1 mg/kg. Mice exposed on PND 3 to 2.22 mg/kg did not show a significant decrease in habituation capability with age. The decrease observed in the habituation capability in the adult mice exposed neonatally to the high dose indicated that the neurotoxic effect of neonatal decaBDE exposure was persistent and also worsened with age. The NOAEL in this study was 2.22 mg/kg, and the lowest-observed-adverse-effect level (LOAEL) was 20.1 mg/kg for significant changes in spontaneous motor behavior and decreased habituation capability for locomotion, rearing, and total activity, worsening with increasing age.

Rice et al. (2007) examined the effects on developmental milestones, sensorimotor behaviors, serum thyroxine (T_4) levels, and locomotor activity in male and female C57BL6/J mice

administered BDE-209 (99.5% purity) from a micropipette in doses of 0, 6, or 20 mg/kg-day from PNDs 2-15. There were no delays in postnatal developmental milestones (pinna detachment, incisor eruption, eye opening, vaginal opening, or testes descent) from BDE-209 treatment in male or female mice. There were no effects of exposure on anogenital distance or crown-rump length.

The authors developed a special functional observational battery (FOB) to examine a series of home-cage, reflexive, and sensorimotor behaviors, measured on PND 14, 16, 18, or 20. Three of the FOB endpoints were affected by BDE-209 exposure at 6 and 20 mg/kg-day: palpebral reflex, forelimb grip, and struggling behavior during handling.

Rice et al. (2007) also examined the locomotor activity of male and female mice in a novel environment over a 2-hour period on PND 70 and at approximately 1 year of age. Locomotor activity declined over the course of the 2-hour assessment in PND 70 males and females in the control and treated groups. However, the rate of decline was significantly different in male mice exposed to 6 and 20 mg/kg-day compared with control animals, an effect that was most pronounced in the high-dose males during the first 1.5 hours of the 2-hour activity session. There was a non-dose-related decline in the locomotor activity in the female mice during the 2-hour activity session. Unlike the males they became hypoactive compared with the controls. There was no effect of BDE-209 treatment on the locomotor activity of the 1-year-old male and female mice. The effect of BDE-209 treatment on serum T_4 in PND 21 offspring was also investigated in this study. A dose-related reduction in serum T_4, in comparison with controls, occurred in males but not in females.

The LOAEL in this study was 6 mg/kg-day, the lowest dose tested, for decrease in the percent of male and female pups performing the palpebral reflex, increased struggling behavior of male mice, decreased T_4 levels in male mice, and effects on locomotor activity of male mice on PND 70.

BDE-209 (>98% purity) in a fat emulsion was administered by gavage to 3-day-old Sprague-Dawley rats at 0, 6.7, or 20.1 mg/kg (Viberg et al., 2007). A total of 20 rats were picked from three to five different litters in each treatment group. Motor activity (locomotion, rearing, and total activity) was measured for a 60-minute period, divided into three 20-minute periods, in rats at the age of 2 months. There were no clinical signs of toxicity in the BDE-209-treated rats at any given time during the experimental period, nor was there any significant difference in body-weight gain or adult weight between controls and rats treated with BDE-209. In control rats at 2 months of age, there was a distinct decrease in locomotion, rearing, and total activity, indicating habituation in response to the diminishing novelty of the test chamber over the 60-minute test period,. Two-month-old rats exposed to 20.1 mg/kg BDE-209 on PND 3 displayed significantly less activity for all three behavioral variables during the first 20-minute

test period compared with controls, while during the third 20-minute period (40-60 minutes) they were significantly more active than the control animals. Rats receiving the low dose of BDE-209 (6.7 mg/kg) showed significantly increased locomotion activity during the second 20-minute period, significantly decreased rearing activity during the first and second 20-minute periods, and significantly higher total activity during the first and second 20-minute periods, compared with the control rats. The LOAEL in this study was 6.7 mg/kg for significant changes in spontaneous motor behavior (locomotion, rearing, and total activity) in 2-month-old rats given BDE-209 on PND 3.

Immediately after the spontaneous behavior tests, nicotine-induced behavior was studied to determine whether changes in spontaneous behavior in adult rats neonatally exposed to BDE 209 included effects on development of the cholinergic system and thereby altered the response in the adult animal to the cholinergic agent nicotine (Viberg et al., 2007). The rats were given a single subcutaneous injection of 80 µg nicotine base/kg, a dose known to cause an increase in activity in experimental animals, and were immediately tested again for nicotine-induced motor behavior with regard to locomotion, rearing, and total activity during another 60 minute period divided into three 20-minute periods.

Pair-wise testing between the nicotine-injected and saline-injected rats showed, as expected, a significant increase in response to nicotine in the neonatally vehicle-treated rats during the first 20-minute period (60-80 minutes) for all three variables (locomotion, rearing, and total activity). In contrast, the nicotine-injected rats exposed to 20.1 mg/kg of BDE-209 on PND 3 showed significantly decreased activity for all three tests (locomotion, rearing, and total activity) during the first 20-minute period (60-80 minutes) compared with the rats neonatally exposed to the high BDE-209 dose and injected with saline. The authors concluded that neonatal exposure to BDE-209 on PND 3 affects adult spontaneous behavior and also affects the cholinergic system, seen as changes in the adult rats' response to the cholinergic agent nicotine.

The NOAEL of 2.22 mg/kg-day identified in the Viberg et al. (2003) study was lower than the LOAELs identified in the neurobehavioral studies conducted by Viberg et al. (2007) and Rice et al. (2007). The Viberg et al. (2003) study was therefore selected as the principal study for deriving the RfD.

I.A.3. UNCERTAINTY FACTORS

UF = 300

A 10-fold UF_A was used to account for laboratory animal to human interspecies differences. Although the toxicokinetics of decaBDE in animals have been evaluated, no adequate

description of toxicokinetics of decaBDE in humans exists. The critical effect for deriving the RfD, altered behavior due to exposure during development, is expected to be relevant to humans. No quantitative data were identified to compare relative human and rodent sensitivity to these changes. However, given the longer period of brain development in humans as compared to rodents and the higher importance of cognitive function, it is appropriate to consider that humans may be more sensitive than rodents in the absence of specific data. Based on these considerations, the default UF_A value of 10 was used in the absence of data.

A default intraspecies UF_H of 10 was applied to account for variations in susceptibility within the human population (intrahuman variability). This factor accounts for the segment of the human population that may be more sensitive than the general population to exposure to BDE 209. A default value is warranted because insufficient information is currently available to assess human-to-human variability in BDE-209 toxicokinetics or toxicodynamics.

A threefold UF_S was used to adjust for exposure duration. For BDE-209, the principal study identified endpoints that, for the most part, reflect specific aspects of developmental physiology. The hypothesized window of susceptibility, proposed by the study authors, is based on the observation that the developmental neurotoxic effects observed following exposure to BDE-209 on PND 3 will not occur once the toxicokinetics of intestinal uptake and excretion have matured and the animal brain is developmentally less active (outside the window of susceptibility). The UF_S was viewed as a dosing duration adjustment rather than simply a comparison of the effects of a subchronic to a chronic exposure. A threefold UF_S was applied because the critical study dosed the animals only once within the hypothesized critical window.

A UF_L for LOAEL-to-NOAEL extrapolation was not applied because a NOAEL was used as the point of departure.

A UF_D to account for deficiencies in the available decaBDE database was not necessary. Available animal studies on repeated oral exposure to decaBDE include 14-day studies in rats and mice (NTP, 1986), 13-week studies in rats and mice (NTP, 1986), and 2-year studies in rats and mice (NTP, 1986). A developmental and behavioral toxicity study in male and female mice was available (Rice et al., 2007), as well as a behavioral study in male rats (Viberg et al., 2007). A 7-week study of sperm functions in mice was also available (Tseng et al., 2006). In addition, a standard developmental toxicity study in rats was identified for decaBDE (Hardy et al., 2002). No multigeneration reproductive toxicity study or other study of reproductive function is available for pure decaBDE. This array of studies results in potential uncertainty regarding the reproductive toxicity of decaBDE. However, this potential uncertainty is adequately accounted for based on the following considerations. First, none of the well-conducted, longer-term dosing studies identified effects on male or female reproductive

organs. Second, no developmental or reproductive effects were observed at doses up to 1,000 mg/kg-day in rats (Hardy et al., 2002) and 100 mg/kg-day in mice (Tseng et al., 2006). The absence of effects in the available longer-term and developmental studies indicates that at least some aspects of reproductive organ toxicity or function are not affected at doses much higher than those that resulted in the neurological effects in neonates (Viberg et al., 2003), although effects on mating and fertility are not evaluated in these studies.

The other potential uncertainty in the database factor is immunotoxicity from exposure to decaBDE. The potential immunotoxicity was indicated by the observations of significant increases in spleen fibrosis and lymphoid hyperplasia in male rats treated with a high dose of decaBDE (NTP, 1986). However, no such changes occurred in female rats or in either sex of treated mice (NTP, 1986). In addition, an in vitro immunotoxicity study (Pullen et al., 2003) with mouse splenocytes suggested that decaBDE is not likely to affect the immune system in an immunosuppressive manner nor the production of the cytokines by these cells. Moreover, the proposed point of departure is based on the developmental neurobehavioral changes and immunotoxicity is not likely to occur at the current point of departure of 2.22 mg/kg, which is 500-fold lower than the NOAEL for histopathological changes in rat spleen and lymphoid in the NTP (1986) study.

I.A.4. ADDITIONAL STUDIES/COMMENTS

NTP (1986) conducted 14-day and 13-week studies in male and female mice and rats. No effects on health, survival, body weights, feed consumption, or compound-related clinical signs or gross pathology were reported. Doses used in the 14-day studies were as high as approximately 22,000 mg/kg-day in mice and 10,000 mg/kg-day in rats. In the 13-week studies, the doses were as high as approximately 11,000 and 3,500 mg/kg-day in mice and rats, respectively.

In a 2-year study, male and female F344/N rats were exposed to decaBDE (94-97% purity) at doses of 0, 1,120, or 2,240 mg/kg-day for male rats and 0, 1,200, or 2,550 mg/kg-day for female rats (NTP, 1986). Exposure to decaBDE in the diet did not cause compound-related effects on survival or any significant effects on body weight or food consumption. However, treatment resulted in several nonneoplastic changes in high-dose males, including thrombosis and degeneration of the liver, fibrosis in the spleen, and lymphoid hyperplasia in the mandibular lymph nodes. Based on these results, a NOAEL for systemic toxicity was 1,120 mg/kg-day, and the LOAEL was 2,240 mg/kg-day. Female rats appeared to be less sensitive to the systemic toxicity of decaBDE, and the NOAEL in female rats was 2,550 mg/kg-day, the highest dose tested.

In a similar 2-year study (NTP, 1986), male and female B6C3F1 mice were administered decaBDE (94-97% purity) in the diet at doses of 0, 3,200, or 6,650 mg/kg-day for male mice and 0, 3,760, or 7,780 mg/kg-day for female mice. DecaBDE treatment caused liver granulomas, liver hypertrophy, and thyroid gland follicular cell hyperplasia in males and stomach ulcers in females. Based on these results, no NOAEL for systemic effects for males was established. Female mice were less sensitive to the systemic toxicity of decaBDE at the doses used in this study; however, the study identified a NOAEL for a portal-of-entry effect for females of 3,760 mg/kg-day and a LOAEL of 7,780 mg/kg-day, based on an increase in the incidence of stomach ulcers.

The following data sets from the NTP (1986) 2-year rat and mouse studies were selected for benchmark dose (BMD) modeling: thrombosis in the liver, liver degeneration, fibrosis in the spleen, and lymphoid hyperplasia in male rats and centrilobular hypertrophy in the livers and follicular cell hyperplasia in the thyroid of male mice. Based on the comparison of BMD modeling results for all the potential critical effects observed in the chronic rat and mouse studies, the lowest bound on the BMD ($BMDL_{10}$) is 406 mg/kg-day for liver degeneration effect in male rats. This value is much higher than the NOAEL of 2.22 mg/kg for the neurobehavioral changes observed in Viberg et al. (2003).

Tseng et al. (2006) studied the effects of BDE-209 on mouse sperm function, DNA content, and histopathology of the testes. CD-1 male mice were fed decaBDE (98% purity) by gavage in corn oil at 0, 10, 100, 500, or 1,500 mg/kg-day from PNDs 21-70. Body weight, body-weight gain, and absolute and relative weights of the testis, epididymis, cauda epididymis, and seminal vesicle of treated animals were not significantly different from controls at sacrifice on PND 71. Morphology of the testicular tissues appeared normal in all treated groups compared with controls. DNA content in testis cells was unaffected by treatment with BDE-209. No significant differences in sperm motility, sperm count, or morphology were seen between the groups exposed to BDE-209 and the controls. Sperm motion velocity parameters were measured, including curvilinear velocity, straight line velocity, and amplitude of the lateral head displacement (ALH). The only effect seen on sperm motion velocity was a significant decrease in ALH at 500 and 1500 mg/kg-day. Significant increase in the generation of hydrogen peroxide in the sperm of sexually mature mice occurred at 500 and 1500 mg/kg-day. The mitochondrial membrane potential (MMP) of sperm cells, a predictor of sperm fertility potential, was also assessed. Mice exposed to 500 and 1,500 mg/kg-day were found to have a significant decrease in high MMP sperm. In addition, the MMP was negatively and significantly associated with the generation of sperm hydrogen peroxide. The NOAEL in this study was 100 mg/kg-day and the LOAEL 500 mg/kg-day for decrease in ALH and MMP and increased generation of hydrogen peroxide in the sperm of adult mice.

In Hardy et al. (2002), Sprague-Dawley rats were administered decaBDE (97% purity) in corn oil by gavage at doses of 0, 100, 300, or 1,000 mg/kg-day during gestation days 0 through 19. Dams were sacrificed on day 20 of gestation, the indices of fertility were recorded, and histological examination of the placenta and fetuses were conducted. No effects were observed in maternal clinical findings, body weight, or body-weight gain. No statistically significant differences were observed in maternal absolute or relative liver weights between treatment and control groups. At necropsy, gross examination of the dams revealed no adverse effect of treatment with decaBDE. Number of dams with viable fetuses, mean number of corpora lutea, number of implantation sites, percent preimplantation loss per dam, number of viable fetuses, and gravid uterine weights were not adversely affected by decaBDE treatment.

A statistically significant increase in the mean number of early resorptions per dam was observed in the 1,000 mg/kg-day group compared with controls. Based on the lack of a consistent dose response for this effect, lack of a statistically significant positive trend associated with the effect, and the high incidence of this effect historically for the laboratory, these effects are not considered to be of toxicological significance. Fetal body weights, crown-rump ratio, and fetal sex ratio were not different between treatment and control groups. No adverse decaBDE treatment-related effects were identified during fetal external, skeletal, or visceral examinations. DecaBDE treatment, therefore, did not produce any evidence of maternal or developmental toxicity up to the highest dose tested of 1,000 mg/kg-day. The NOAEL for maternal and developmental toxicity in this study was 1,000 mg/kg-day.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.A.5. CONFIDENCE IN THE ORAL RfD

Study -- Low
Data Base -- Medium
RfD -- Low

The overall confidence in this RfD assessment is low. Confidence in the principal study (Viberg et al., 2003) is low. The dosing regimen did not include gestation and lactation exposure; only single doses were given. The study was conducted in male mice only. The protocol was unique and did not conform to health effects test guidelines for neurotoxicity screening battery or developmental neurotoxicity studies. While the study design appears to identify a developmental window of susceptibility, it is not adequate to determine the effect of longer dosing. Translating the implications of these data to more traditional dosing regimens is problematic, particularly with regard to evaluating the implications of in utero and postnatal exposure.

Another concern is that, based on the data provided in the published report (Viberg et al., 2003), more than one pup per litter was used for the behavioral testing (10 male mice were randomly selected from three to five different litters in each treatment group). Increasing the number of samples from each litter may bias the analyses towards false positives. Another concern regarding the study design was the limited number of neurobehavioral parameters that were assessed; the authors measured only indices related to motor activity (locomotion, rearing, and total activity). The absence of a full FOB that evaluates neurological and behavioral signs limits the ability to correlate the reported effects with other FOB parameters. Data from the FOB utilized in the Rice et al. (2007) study, also in mice, mitigate some concern related to its absence in the Viberg et al. (2003) study.

As indicated in the *Guidelines for Neurotoxicity Risk Assessment* (U.S. EPA, 1998), it is assumed that an agent that produces detectable adverse neurotoxic effects in experimental animal studies will pose a potential hazard to humans. For BDE-209, in the absence of human evidence, data from experimental animal studies are used as the basis for the RfD.

While study design limitations cloud the utility of this study, several additional considerations support the use of these data. The fact that the effects were observed after a single dose is a situation that increases concern regarding the impact of BDE 209 on neurological development. Acute exposure to a highly lipophilic chemical, such as BDE-209, will result in exposure that lasts much longer than just acutely. In addition, there are a wide variety of brain structures that have very limited critical windows during development. These short critical windows translate to susceptible periods of exposure that can be very short.

The concept that exposure during critical periods of development can induce functional neurological effects later in development has been demonstrated with structurally related polybrominated diphenyl ether (PBDE) congeners, including tetra-, penta-, and hexaBDEs. In addition, the study of Rice et al. (2007) strengthens the evidence that links the behavioral effects seen in mice to neonatal BDE-209 exposure. Therefore, the observed neurobehavioral effects in the Viberg et al. (2003) study in mice and the Viberg et al. (2007) study in rats are biologically plausible, and exposure to BDE-209 may pose a potential hazard to humans (U.S. EPA, 1998).

The available database included less-than-lifetime and chronic studies in two species (NTP, 1986). There are developmental and reproductive studies (Rice et al., 2007; Viberg et al., 2007; Tseng et al., 2006; Hardy et al., 2002) in addition to the critical neurobehavioral study. The confidence in the database is medium.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.A.6. EPA DOCUMENTATION AND REVIEW OF THE ORAL RfD

Source Document — U.S. EPA (2008).

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)* (U.S. EPA, 2008). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).***

Agency Completion Date -- 06/30/2008

I.A.7. EPA CONTACTS

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 (email address).

I.B. REFERENCE CONCENTRATION (RfC) FOR INHALATION EXPOSURE

Substance Name — 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)
CASRN — 1163-19-5
Last Revised — 06/30/2008

The RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. The RfC considers toxic effects for both the respiratory system (portal of entry) and for effects peripheral to the respiratory system (extrarespiratory effects). The inhalation RfC (generally expressed in units of mg/m^3) is analogous to the oral RfD and is similarly intended for use in risk assessments for health effects known or assumed to be produced through a nonlinear (presumed threshold) mode of action.

Inhalation RfCs are derived according to *Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry* (U.S. EPA, 1994). Because RfCs can

also be derived for the noncarcinogenic health effects of substances that are carcinogens, it is essential to refer to other sources of information concerning the carcinogenicity of this chemical 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.B.1. INHALATION RfC SUMMARY

No data are available for deriving a reference concentration for BDE-209.

I.B.2. PRINCIPAL AND SUPPORTING STUDIES

Not applicable.

I.B.3. UNCERTAINTY FACTORS

Not applicable.

I.B.4. ADDITIONAL STUDIES/COMMENTS

Not applicable.

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

I.B.5. CONFIDENCE IN THE INHALATION RfC

Not applicable.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

I.B.6. EPA DOCUMENTATION AND REVIEW OF THE INHALATION RfC

Source Document -- U.S. EPA (2008)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the *Toxicological Review of 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)* (U.S. EPA, 2008). ***To review this***

***appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF)*.**

Agency Completion Date -- 06/30/2008

I.B.7. EPA CONTACTS

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 (email address).

II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name — 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)
CASRN — 1163-19-5
Section II. Last Revised — 06/30/2008

This section provides information on three aspects of the carcinogenic assessment for the substance in question: the weight-of-evidence judgment of the likelihood that the substance is a human carcinogen, and quantitative estimates of risk from oral and inhalation exposure. Users are referred to Section I of this file for information on long-term toxic effects other than carcinogenicity.

The rationale and methods used to develop the carcinogenicity information in IRIS are described in the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) and the *Supplemental Guidance for Assessing Susceptibility from Early-Life Exposure to Carcinogens* (U.S. EPA, 2005b). The quantitative risk estimates are derived from the application of a low-dose extrapolation procedure, and are presented in two ways to better facilitate their use. First, route-specific risk values are presented. The "oral slope factor" is a plausible upper bound on the estimate of risk per mg/kg-day of oral exposure. Similarly, a "unit risk" is a plausible upper bound on the estimate of risk per unit of concentration, either per µg/L drinking water (see Section II.B.1.) or per $\mu g/m^3$ air breathed (see Section II.C.1.). Second, the estimated concentration of the chemical substance in drinking water or air when associated with cancer risks of 1 in 10,000, 1 in 100,000, or 1 in 1,000,000 is also provided.

II.A. EVIDENCE FOR HUMAN CARCINOGENICITY

II.A.1. WEIGHT-OF-EVIDENCE CHARACTERIZATION

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), the database for decabromodiphenyl ether provides *suggestive evidence of carcinogenic potential*. The weight of evidence of human carcinogenicity of decaBDE is based on (1) no studies of cancer in humans exposed to decaBDE; (2) statistically significant increases in incidence of neoplastic nodules in the liver of low- and high-dose male rats and high-dose female rats; (3) significantly increased incidences of hepatocellular adenoma or carcinoma (combined) in male mice at the low dose and marginally increased incidences at the high dose; (4) nonsignificantly increased incidences of hepatocellular adenoma or carcinoma (combined) in female mice; (5) slightly greater (but not statistically significant) incidences of thyroid gland adenomas or carcinomas (combined) in dosed male and female mice; (6) significantly increased incidences in male mice, at both doses, of follicular cell hyperplasia, considered by many as a precursor to thyroid tumors; and (7) an apparent absence of genotoxic potential.

The *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a) state: "When there is suggestive evidence, the Agency generally would not attempt a dose-response assessment, as the nature of the data generally would not support one; however, when the evidence includes a well-conducted study, quantitative analyses may be useful for some purposes, for example, providing a sense of the magnitude and uncertainty of potential risks, ranking potential hazards, or setting research priorities. In each case, the rationale for the quantitative analysis is explained, considering the uncertainty in the data and the suggestive nature of the weight of evidence. These analyses generally would not be considered Agency consensus estimates."

In this case, the weight of experimental evidence is on the strong end of the spectrum for the descriptor suggestive evidence of carcinogenic potential, since there is some evidence that decaBDE is carcinogenic in more than one species, sex, and site. In chronic rodent studies support for tumorigenic effects in the liver was found in both sexes of rats and mice. Similarly, although the increases in thyroid tumors were not statistically significant in either sex of mice, they were supported by increases in a precursor to thyroid tumors, follicular cell hyperplasia. The cancer bioassays for decaBDE are generally well-conducted and the data from these studies are adequate to support a quantitative cancer dose-response assessment. Considering these data and uncertainty associated with the suggestive nature of the tumorigenic response, EPA concluded that quantitative analyses may be useful for providing a sense of the magnitude of potential carcinogenic risk. Based on the weight of evidence, a dose-response assessment of the carcinogenicity of decaBDE is deemed appropriate.

The carcinogenicity of decabromodiphenyl ether was evaluated in IRIS in 1989. DecaBDE was classified in Group C, *possible human carcinogen*, according to EPA cancer guidelines (U.S. EPA, 1986). The basis of this classification was lack of human carcinogenicity data and

limited evidence of carcinogenicity in animals, namely, significantly increased incidences of neoplastic liver nodules in male and female rats and increased incidences of hepatocellular adenomas or carcinomas (combined) in male mice (NTP, 1986). A quantitative estimate of carcinogenic risk from oral exposure was not derived in this IRIS assessment.

For more detail on Characterization of Hazard and Dose Response, exit to the toxicological review, Section 6 (PDF).

For more detail on Susceptible Populations, exit to the toxicological review, Section 4.7 (PDF).

II.A.2. HUMAN CARCINOGENICITY DATA

No information is available on the carcinogenicity of decaBDE in humans.

II.A.3. ANIMAL CARCINOGENICITY DATA

Groups of male and female F344/N rats were exposed to decaBDE (94-97% purity) in the diet at doses of 0, 1,120, or 2,240 mg/kg-day for male rats and 0, 1,200, or 2,550 mg/kg-day for female rats (NTP, 1986). No clinical signs of toxicity were observed in the treated rats. Statistically significant increases in the incidence of neoplastic nodules in the liver were observed at both treatment doses in males and at the high dose in females, providing some evidence of carcinogenicity of decaBDE. The incidence of hepatocellular carcinomas was low in male and female rats.

At the time the NTP (1986) study was conducted, the term neoplastic nodule was used to describe abnormal cellular masses in the livers of rats, characterized by loss or distortion of normal cellular architecture (Maronpot et al., 1986). Some of those nodules would now be described as benign hepatocellular adenomas in rats (Wolf and Mann, 2005). However, there is no complete equivalency between the neoplastic nodule of the past and hepatocellular adenoma term of today. Some of the neoplastic nodules from the NTP (1986) study might now be classified as foci of cellular alteration or hyperplasia rather than adenomas (Maronpot et al., 1986). Adenomas and foci of cellular alteration are considered to be preneoplastic lesions, whereas hyperplastic lesions represent secondary nonneoplastic changes (Maronpot et al., 1986). The assumption that the hepatic neoplastic nodules from the NTP (1986) bioassay are equivalent to hepatic adenomas under the current NTP lexicon is a conservative interpretation of the data.

Groups of male and female B6C3F1 mice were administered decaBDE (94-97% purity) in the diet at doses of 0, 3,200, or 6,650 mg/kg-day in male mice and 0, 3,760, or 7,780 mg/kg-day in

female mice. No clinical signs of toxicity were observed in the treated mice. The combined incidence of hepatocellular adenomas or carcinomas in male mice significantly increased at low dose and increased marginally at high dose. In the thyroid gland, significant increases in the incidence of follicular cell hyperplasia, considered by many as a precursor to thyroid tumors, was observed in males but not in females. Thyroid gland follicular cell adenomas or carcinomas (combined) were slightly, but not significantly, increased in treated mice of both sexes over the corresponding control mice.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

DecaBDE was not mutagenic in *Salmonella typhimurium* TA98, TA100, TA1535, or TA1537 strains in the presence or absence of exogenous metabolic system; it did not induce sister-chromatid exchanges or chromosomal aberrations in Chinese hamster ovary cells in the absence or presence of exogenous metabolic system (NTP, 1986).

II.B. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM ORAL EXPOSURE

II.B.1. SUMMARY OF RISK ESTIMATES

II.B.1.1. Oral Slope Factor - 0.0007 per mg/kg-day*

The oral slope factor is derived from the LED_{12}, the 95% lower bound on the exposure associated with a 12% extra cancer risk, by dividing the risk (as a fraction) by the LED_{12}, and represents an upper bound, continuous lifetime exposure risk estimate:

LED_{12}, lower 95% bound on exposure at 12% extra risk = 178 mg/kg-day. The slope of the linear extrapolation from the LED_{12} = 0.12/178 mg/kg-day = 0.0007 per mg/kg-day.

ED_{12}, central estimate of exposure at 12% extra risk = 263 mg/kg-day. The slope of the linear extrapolation from the ED_{12} = 0.12/263 mg/kg-day = 0.0005 per mg/kg-day.

* The term neoplastic nodule is no longer used for rat liver tumors, and it is not possible to know if all lesions originally categorized as neoplastic nodules would now be described as benign hepatocellular adenomas or preneoplastic hyperplasia under current guidelines. Accordingly, there is some uncertainty in the calculated slope factor that should be considered when it is applied in a quantitative risk assessment. In this case, if the neoplastic nodules

would now be described as preneoplastic hyperplasia, then the derivation of a cancer slope factor based on increased incidence of neoplastic nodules could result in an overestimate of risk. Overall, the risk presented is considered a plausible upper bound.

II.B.1.2. Drinking Water Unit Risk - 2E-8 per µg/L*

Drinking Water Concentrations at Specified Risk Levels

Risk Level	Lower Bound on Concentration Estimate*
E-4 (1 in 10,000)	5,000 µg/L
E-5 (1 in 100,000)	500 µg/L
E-6 (1 in 1,000,000)	50 µg/L

* The unit risk and concentration estimates assume water consumption of 2 L/day by a 70 kg human. The term neoplastic nodule is no longer used for rat liver tumors, and it is not possible to know if all lesions originally categorized as neoplastic nodules would now be described as benign hepatocellular adenomas or preneoplastic hyperplasia under current guidelines. Accordingly, there is some uncertainty in the calculated slope factor that should be considered when it is applied in a quantitative risk assessment. In this case, if the neoplastic nodules would now be described as preneoplastic hyperplasia, then the derivation of a cancer slope factor based on increased incidence of neoplastic nodules could result in an overestimate of risk. Overall, the risk presented is considered a plausible upper bound.

II.B.1.3. Extrapolation Method

Multistage model with linear extrapolation from the point of departure (LED_{12}).

II.B.2. DOSE-RESPONSE DATA

Tumor Type -- Liver neoplastic nodules or carcinoma (combined)
Test Species -- Male F344/N rats
Route -- Oral, diet
Reference -- NTP (1986)

Drinking Water Concentrations at Specified Risk Levels

Administered dose (mg/kg-day)	Human equivalent dose[a] (mg/kg-day)	Incidence of liver neoplastic nodules and carcinomas (combined)
0	0	2/50 (4%)
1120	305	8/50 (16%)
2240	608	15/49 (31%)

*A body weight $(bw)^{3/4}$ scaling factor was used to convert the administered dose in the rat study to human equivalent dose (HED): HED=administered dose x $(body\ weight\ of\ animal/body\ weight\ of\ human)^{.25}$. Body weight of human is assumed to be 70 kg. Body weights of rats were calculated from reported weekly body weight data.

II.B.3. ADDITIONAL COMMENTS

Although no human studies were available, two chronic rodent studies provide suggestive evidence of decaBDE-induced carcinogenicity. The data from these studies are adequate to support a quantitative cancer dose-response assessment. Even though the available evidence is suggestive of human carcinogenic potential and there is uncertainty about the classification of the neoplastic nodules as precancerous growths, there is very limited information exploring the mode of action for any of the tumors reported in the animal chronic studies. While decaBDE was not mutagenic or genotoxic in limited in vitro studies, there are no in vivo studies of genotoxic potential and the data are inadequate to support alternative mode-of-action hypotheses. In the absence of such data, extrapolation from the point of departure to lower doses is conducted by using a linear approach.

Based on a comparison of estimated effective doses for all the cancer endpoints observed in rat and mouse chronic studies (NTP, 1986), the neoplastic nodules or carcinomas (combined) in the liver of treated male rats are the most sensitive endpoint. Therefore, the LED_{12} of 178 mg/kg-day estimated for this endpoint is used as a point of departure for calculating cancer slope factor.

For linear extrapolation, a straight line is drawn from the point of departure expressed as a human equivalent dose to the origin to give a probability of extra risk. The slope of the line expresses extra risk per dose unit. For linear extrapolation, the slope of the line is $0.12/LED_{12}$. For neoplastic nodules or carcinomas, the resulting oral cancer slope factor is 0.0007 per mg/kg-day (7E-4 per mg/kg-day).

II.B.4. DISCUSSION OF CONFIDENCE

Two doses at adequately high levels and a sufficient number of mice and rats were tested in the NTP (1986) study. In addition, the purity of the decaBDE used was 94-97%, with no detectable brominated dioxins or furans. The major impurities in the decaBDE test material were identified as two unspecified congeners of nonabromodiphenyl ether.

Slope factors were calculated from six data sets based on hepatic neoplastic nodules and combined hepatic neoplastic nodules/carcinomas in male and female rats and on thyroid follicular cell hyperplasia and hepatic adenomas or carcinomas (combined) in male mice with doses ranging from 4E-4 per mg/kg-day to 7E-4 per mg/kg-day.

The term neoplastic nodule is no longer used for rat liver tumors, and it is not possible to know if all lesions originally categorized as neoplastic nodules would now be described as benign hepatocellular adenomas or preneoplastic hyperplasia under current guidelines. Accordingly, there is some uncertainty in the calculated slope factor that should be considered when it is applied in a quantitative risk assessment. In this case, if the neoplastic nodules would now be described as preneoplastic hyperplasia, then the derivation of a cancer slope factor based on increased incidence of neoplastic nodules could result in an overestimate of risk. Overall, the risk presented is considered a plausible upper bound.

II.C. QUANTITATIVE ESTIMATE OF CARCINOGENIC RISK FROM INHALATION EXPOSURE

II.C.1. SUMMARY OF RISK ESTIMATES

Not applicable.

II.C.2. DOSE-RESPONSE DATA

Not applicable.

II.C.3. ADDITIONAL COMMENTS

Not applicable.

II.C.4. DISCUSSION OF CONFIDENCE

Not applicable.

II.D. EPA DOCUMENTATION, REVIEW, AND CONTACTS (CARCINOGENICITY ASSESSMENT)

II.D.1. EPA DOCUMENTATION

Source Document -- U.S. EPA (2008)

This document has been reviewed by EPA scientists, interagency reviewers from other federal agencies, and the public, and peer reviewed by independent scientists external to EPA. A summary and EPA's disposition of the comments received from the independent external peer reviewers and from the public is included in Appendix A of the T*oxicological Review of 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)* (U.S. EPA, 2008). ***To review this appendix, exit to the toxicological review, Appendix A, Summary of External Peer Review and Public Comments and Disposition (PDF).***

II.D.2. EPA REVIEW

Agency Completion Date -- 06/30/2008

II.D.3. EPA CONTACTS

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 (email address).

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

VI. BIBLIOGRAPHY

Substance Name — 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)
CASRN — 1163-19-5

VI.A. ORAL RfD REFERENCES

Hardy, ML; Schroeder, R; Biesemeier, J; et al. (2002) Prenatal oral (gavage) developmental toxicity study of decabromodiphenyl oxide in rats. Int J Toxicol 21(2):83-91.

Kociba, RJ; Frauson, LO; Humiston, CG; et al. (1975) Results of a two-year dietary feeding study with decabromodiphenyl oxide (DBDPO) in rats. J Combust Toxicol 2:267-285.

NTP (National Toxicology Program). (1986) Toxicology and carcinogenesis studies of decabromodiphenyl oxide (CAS No. 1163-19-5) in F344/N rats and B6C3F1 mice (feed studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR 309. Available from the National Institute of Environmental Health Sciences, Research Triangle Park, NC, and online at http://ntp.niehs.nih.gov/ntp/htdocs/LTrpts/tr309.pdf.

Pullen, S; Boecker, R; Tieg, G. (2003) The flame retardants tetrabromobisphenol A and tetrabromobisphenol A bisallylether suppress the induction of interleukin-2 receptor A chain (CD25) in murine splenocytes. Toxicology 184:11-22.

Rice, DC; Reeve, EA; Herlihy, A; et al. (2007) Developmental delays and locomotor activity in the C57BL6/J mouse following neonatal exposure to the fully-brominated PBDE, decabromodiphenyl ether. Neurotoxicol Teratol 29:511-520.

Tseng, LH; Lee, CW; Pan, MH; et al. (2006) Postnatal exposure of the male mouse to 2,2',3,3',4,4',5,5',6,6'-decabrominated diphenyl ether: decreased epididymal sperm functions without alterations in DNA content and histology in testis. Toxicology 224:33-43.

U.S. EPA (Environmental Protection Agency). (1998) Guidelines for neurotoxicity risk assessment. Fed Regist 63:26926-26954. Available online at http://www.epa.gov/raf/publications/guidelines-neurotoxicity-risk-assessment.htm.

U.S. EPA. (2008) Toxicological review of 2,2',3,3',4,4',5,5',6,6'-decabromodiphenyl ether (BDE-209). Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris.

Viberg, H; Fredriksson, A; Jakobsson, E; et al. (2003) Neurobehavioral derangements in adult mice receiving decabromodiphenyl ether (PBDE 209) during a defined period of neonatal brain development. Toxicol Sci 76:112-120.

Viberg, H; Fredriksson, A; Eriksson, P. (2007) Changes in spontaneous behavior and altered response to nicotine in the adult rat, after neonatal exposure to the brominated flame retardant, decabrominated diphenyl ether (PBDE 209). Neurotoxicol 28:136-142.

VI.B. INHALATION RfC REFERENCES

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH; EPA/600/8-90/066F. Available from the National Technical Information Service, Springfield, VA, PB2000-500023, and online at http://cfpub.epa.gov/ncea/raf/recordisplay.cfm?deid=71993.

U.S. EPA. (2008) Toxicological review of 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209). Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris.

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

Maronpot, RR; Montgomery, CA; Boorman, GA; et al. (1986) National Toxicology Program nomenclature for hepatoproliferative lesions of rats. Toxicol Pathol 14(2):263-273.

NTP (National Toxicology Program). (1986) Toxicology and carcinogenesis studies of decabromodiphenyl oxide (CAS No. 1163-19-5) in F344/N rats and B6C3F1 mice (feed studies). Public Health Service, U.S. Department of Health and Human Services; NTP TR 309. Available from the National Institute of Environmental Health Sciences, Research Triangle Park, NC, and online at http://ntp.niehs.nih.gov/ntp/htdocs/LTrpts/tr309.pdf.

U.S. EPA. (1986) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/R-00/0004.

U.S. EPA. (2005a) Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001B. Available from: http://www.epa.gov/iris/backgrd.html.

U.S. EPA. (2005b) Supplemental guidance for assessing susceptibility from early-life exposure to carcinogens. Risk Assessment Forum, Washington, DC; EPA/630/R-03/003F. Available online at http://www.epa.gov/cancerguidelines.

U.S. EPA. (2008) Toxicological review of 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209). Integrated Risk Information System (IRIS), National Center for Environmental Assessment, Washington, DC. Available online at http://www.epa.gov/iris.

Wolf, DC, Mann, PC (2005) Confounders in interpreting pathology for safety and risk assessment. Toxicol Appl Pharmacol 202:302-308.

VII. REVISION HISTORY

Substance Name — 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)
CASRN — 1163-19-5
File First On-Line 01/31/1987

Date	Section	Description
12/01/1989	II.	Carcinogen assessment on-line
10/28/2003	I.A.6., II.D.2.	Screening-Level Literature Review Findings message has been added.
06/30/2008	I., II., VI.	RfD, RfC, and cancer assessment sections updated

VIII. SYNONYMS

Substance Name — 2,2',3,3',4,4',5,5',6,6'-Decabromodiphenyl ether (BDE-209)
CASRN — 1163-19-5
Section VIII. Last Revised — 06/30/2008

- Benzene, 1,1'-oxybis(2,3,4,5,6-pentabromo-

- BDE-209
- DBDPE
- DBDPO
- DecaBDE
- Decabromobiphenyl ether
- Decabromobiphenyl oxide
- Decabromodiphenyl ether
- Decabromodiphenyl oxide
- Decabromophenyl ether
- Ether, bis(pentabromophenyl)
- Ether, decabromodiphenyl
- Pentabromophenyl ether