

2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE-153); CASRN 68631-49-2

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',4,4',5,5'-HEXABROMODIPHENYL ETHER (BDE-153)
CASRN -- 68631-49-2

File First On-Line 06/30/2008

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

The hexabromodiphenyl ether congener 2,2',4,4',5,5'-hexabromodiphenyl ether (BDE-153) has not been previously assessed in IRIS. A health assessment of the hexabromodiphenyl ether homolog group (CASRN 36483-60-0) was previously entered on IRIS on 08/01/1990.

Information was not available to derive an RfD or RfC or to assess the carcinogenic potential of the hexabromodiphenyl ether homolog group.

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

Substance Name — 2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE-153)
CASRN — 68631-49-2

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: 0.45 mg/kg	3000	0.0002 mg/kg-day
Single dose gavage study in mice Viberg et al., 2003	LOAEL: 0.9 mg/kg		

I.A.2. PRINCIPAL AND SUPPORTING STUDIES

There is only one study available for dose-response assessment and derivation of an RfD for BDE-153. The Viberg et al. (2003) study was conducted to determine whether habituation (spontaneous motor behavior in a novel environment), learning, and memory are affected in adult mice after neonatal exposure to BDE-153. Another objective of this study was to investigate whether such neonatal exposure can affect the development of the cholinergic system by reducing the density of nicotinic receptors in the hippocampus of the mouse brain at approximately 6 months of age. Male neonatal NMRI mice were given single doses of BDE-153 (92.5% BDE-153; 7.5% heptaBDE-183) by gavage on postnatal day (PND) 10 at doses of 0, 0.45, 0.9, or 9.0 mg/kg, dissolved in a fat emulsion. Motor activity was measured for a 60-minute period, divided into three 20-minute periods, in male mice at ages 2, 4, and 6 months. The tests were conducted in 10 mice randomly selected from the three to five litters that comprised each dose group at 2, 4, and 6 months of age. Motor activity tests measured

locomotion (horizontal movement), rearing (vertical movement), and total activity (all types of vibration within the test cage [i.e., those caused by mouse movements, shaking/tremors, and grooming]). From the spontaneous motor behavior test, an habituation ratio was calculated between the performance periods 40-60 minutes and 0-20 minutes for the three different variables (locomotion, rearing, total activity). This ratio was used to analyze alteration in habituation among 2-, 4-, and 6-month-old mice.

There were no clinical signs of toxicity in the BDE-153 treated mice at any given time during the experimental period, nor was there any significant difference in body-weight gain or adult weight between controls and mice treated with BDE-153. In control mice, there was a distinct decrease in locomotion, rearing, and total activity at 2, 4, and 6 months of age, indicating habituation in response to the diminishing novelty of the test chamber over the 60-minute test period. Two-month-old mice exposed to 9.0 mg/kg BDE-153 displayed significantly less activity for all three test 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 ($p \leq 0.01$). Mice receiving 0.9 mg/kg BDE-153 showed significantly lower activity during the first 20-minute period for the rearing and total activity variables compared with the controls, but, during the third 20-minute period, they showed a significantly higher activity compared with the control animals for the two behavioral variables, locomotion and total activity. No effects in activity for any of the three behavioral variables were seen in mice receiving 0.45 mg/kg BDE-153 compared with controls.

At 4 months of age, mice exposed to 9.0 mg/kg BDE-153 displayed the same pattern of activity (hypoactive during the first 20 minutes and hyperactive during the last 20 minutes) for all three behavioral variables: rearing, locomotion, and total activity. Mice receiving 0.9 mg/kg BDE-153 showed significantly lower activity during the first 20-minute period for rearing and total activity compared with the controls, but, during the third 20-minute period, they showed a significantly higher activity compared with the control animals for locomotion and total activity. No effects in activity for any of the three behavioral variables were seen in mice receiving 0.45 mg/kg BDE-153 compared with controls.

Six months after neonatal exposure to BDE-153, the only effect seen in mice receiving the lowest dose of BDE-153 (0.45 mg/kg) was a marginal decrease in total activity during the first 20-minute period, compared with controls. However, since the total activity returned to control levels during the last 20-minute period, this effect was considered of marginal significance. At 9.0 mg/kg, 6-month-old mice were significantly hypoactive and significantly hyperactive during the first and last 20-minute periods, respectively, for all three variables compared with controls. Mice receiving 0.9 mg/kg were significantly less active and more active during the first and last 20-minute period, respectively, for rearing compared with controls. They were also significantly more active compared with controls for locomotion and

total activity during the last 20-minute period of the test but were not significantly hypoactive during the first 20-minute period.

The habituation capability in 2-, 4-, and 6-month-old mice concerning locomotion, rearing and total activity decreased significantly with age at 0.9 and 9.0 mg/kg BDE-153 compared to controls. The LOAEL based on changes in spontaneous motor behavior, worsening with increasing age, was 0.9 mg/kg, and the NOAEL was 0.45 mg/kg.

Viberg et al. (2003) also reported observations for the Morris swim maze test performed at 6 months of age in groups of 19-24 mice from each treatment group. This test was used to assess spatial learning ability and memory by measuring latencies in locating a submerged platform during the acquisition period (days 1-4) and during the reversal learning period on the fifth day. Mice exposed to BDE-153 at 0.9 and 9.0 mg/kg showed significantly longer latencies in locating the platform for the trials on days 2 through 4 of the acquisition period, compared with controls and mice exposed to 0.45 mg/kg. On day 5, after the platform was relocated in order to measure relearning ability in reversal trials, control mice and the 0.45 mg/kg dose groups displayed significantly ($p \leq 0.001$) longer latencies for finding the location of the platform in its new position. This is a normal behavior during relearning, since the mouse initially searches close to the previous location of the platform. Mice exposed to 0.9 and 9.0 mg/kg BDE-153 did not show any significant decrease in latency in the first trial on day 5. However, the latency observed with the fifth trial on day 5 was significantly ($p \leq 0.05$) longer than that of the controls for the 0.9 and 9.0 mg/kg BDE-153 exposed groups.

Changes in the cholinergic receptors have been proposed to affect learning and memory. For this reason, one week after completion of the behavioral tests, six to nine mice in the control, 0.9, and 9.0 mg/kg groups were sacrificed, and measurement of nicotine-binding sites in the hippocampus was performed by using tritium-labeled α -bungarotoxin, a snake neurotoxin that specifically binds to nicotinic cholinergic receptors. Density of nicotinic receptors in the hippocampus of controls and 0.9 mg/kg 6-month-old mice was not affected but was significantly decreased in mice given 9.0 mg/kg, a dose at which mice showed significant defects in learning and memory. The authors hypothesized that such changes in the cholinergic system may be one mechanism behind the neurodevelopmental effects of BDE-153.

The NOAEL for BDE-153 in this study was 0.45 mg/kg, and the LOAEL was 0.9 mg/kg for changes in spontaneous motor behavior, worsening with increasing age, and for effects on learning and memory ability as displayed in the Morris swim maze test. Data for the three spontaneous behavior variables, horizontal movement, vertical movement and total activity, and habituation ratio are only available in graphic form and could not be used for quantitative dose-response assessment.

IA.3. UNCERTAINTY FACTORS

$$UF = 3,000$$

A total uncertainty factor (UF) of 3,000 was applied to the NOAEL of 0.45 mg/kg identified in the Viberg et al. (2003) study: 10 for extrapolating animal data to humans (UF_A interspecies variability), 10 for susceptible human subpopulation (UF_H interhuman variability), 3 for extrapolating from a single dose to a lifetime exposure duration (UF_S), and 10 to account for a deficient database (UF_D).

A 10-fold UF_A was used to account for laboratory animal to human interspecies differences. Although the toxicokinetics of BDE-153 in animals have been evaluated, no adequate description of toxicokinetics of BDE-153 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 applied.

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 153. A default value is warranted because insufficient information is currently available to assess human-to-human variability in BDE-153 toxicokinetics or toxicodynamics.

A UF_S of 3 was used to account for uncertainties in extrapolating from effects seen in a single exposure neurodevelopmental study to a lifetime exposure. Exposure on PND 10 occurred during a period of rapid brain development in mice. Brain development does not continue at an equivalent rate over a mouse's lifespan and is more quiescent during adult life stages. Many brain structures have a very limited critical window during development in early life. Following BDE 153 exposure, toxicokinetic data suggest that a mouse urinary protein becomes functional some time between PNDs 28 and 40, which leads to an increase in BDE 153 urinary excretion, especially in males. This increased excretion reduces the total body burden of BDE, including the levels of radiolabel reaching the brain 24 hours after dosing in older mice compared with that in younger mice. These data thus suggest that the risk of neurodevelopmental effects in neonatal mice may be greater than in older mice because of rapid postnatal brain growth and coincident increased retention of BDE 153 and/or its metabolites. Therefore, chronic exposure is not expected to result in more serious effects.

However because the mice received only a single dose rather than repeated doses over multiple days within the hypothesized critical window, a threefold UF was applied.

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

A UF_D of 10 was used to account for database uncertainty. The available oral database for BDE 153 lacks prenatal developmental neurotoxicity studies, reproductive toxicity studies, and standard chronic or subchronic studies of systemic toxicity. Uncertainties regarding the effects of exposures during the prenatal period, extended postnatal exposures, and latent expression of early postnatal changes in the brain are addressed as a component of the database UF.

Application of a total UF of 3,000 to the NOAEL of 0.45 mg/kg results in a reference dose for BDE-153 of 0.0002 mg/kg-day.

I.A.4. ADDITIONAL STUDIES/COMMENTS

Additional studies on the toxicity of BDE-153 are not available.

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 -- Low
RfD -- Low

Confidence in the Viberg et al. (2003) study is low because the study was conducted in male mice only, the protocol was unique and did not conform to health effects test guidelines for a neurotoxicity screening battery or developmental neurotoxicity studies, the dosing regimen did not include gestation and lactation exposure, more than one pup per litter was used for the behavioral testing, and only single doses were given. Confidence in the database is low because it lacks prenatal developmental neurotoxicity studies, reproductive toxicity studies, and standard chronic or subchronic studies of systemic toxicity. As a result, the overall confidence in the RfD is low.

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',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153)* (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',4,4',5,5'-Hexabromodiphenyl ether (BDE-153)

CASRN — 68631-49-2

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/m³) 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-153.

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',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153)* (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

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II. CARCINOGENICITY ASSESSMENT FOR LIFETIME EXPOSURE

Substance Name — 2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE-153)

CASRN — 68631-49-2

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 µg/m³ 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

Epidemiological studies of exposure to BDE-153 and cancer occurrence in humans are not available. Animal chronic toxicity/carcinogenicity studies have not been conducted with BDE 153, and information is not available on its genotoxicity.

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

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005a), there is "inadequate information to assess the carcinogenic potential" of 2,2',4,4',5,5'-hexabromodiphenyl ether.

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

Not available.

II.A.3. ANIMAL CARCINOGENICITY DATA

Not available.

II.A.4. SUPPORTING DATA FOR CARCINOGENICITY

Not applicable.

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

II.B.1. SUMMARY OF RISK ESTIMATES

Not applicable.

II.B.2. DOSE-RESPONSE DATA

Not applicable.

II.B.3. ADDITIONAL COMMENTS

Not applicable.

II.B.4. DISCUSSION OF CONFIDENCE

Not applicable.

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 *Toxicological Review of 2,2',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153)* (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',4,4',5,5'-Hexabromodiphenyl ether (BDE-153)
CASRN — 68631-49-2

VI.A. Oral RfD References

U.S. EPA. (2008) Toxicological Review of 2,2',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153) in Support of Summary Information on the Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line at <http://www.epa.gov/iris>.

Viberg, H; Frederiksson, A; Eriksson, P. (2003) Neonatal exposure to polybrominated diphenyl ether (PBDE 153) disrupts spontaneous behaviour, impairs learning and memory, and decreases hippocampal cholinergic receptors in adult mice. *Toxicol Appl Pharmacol* 192(2):95-106.

VI.B. INHALATION RfC REFERENCES

U.S. EPA. (1994) Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. Office of Research and Development, Washington, DC; EPA/600/8-90/066F. Available from: National Technical Information Service, Springfield, VA; PB2000-500023, and <http://www.epa.gov/iris/backgrd.html>.

U.S. EPA. (2008) Toxicological Review of 2,2',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153) in Support of Summary Information on the Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line at <http://www.epa.gov/iris>.

VI.C. CARCINOGENICITY ASSESSMENT REFERENCES

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 from: <http://www.epa.gov/iris/backgrd.html>.

U.S. EPA. (2008) Toxicological Review of 2,2',4,4',5,5'-Hexabromodiphenyl Ether (BDE-153) in Support of Summary Information on the Integrated Risk Information System (IRIS). National Center for Environmental Assessment, Washington, DC. Available on line at <http://www.epa.gov/iris>.

VII. REVISION HISTORY

Substance Name — 2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE-153)
CASRN — 68631-49-2
File First On-Line - 06/30/2008

Date	Section	Description
06/30/2008	I., II.	RfD, RfC, and cancer assessment first on line

VIII. SYNONYMS

2,2',4,4',5,5'-Hexabromodiphenyl ether (BDE-153)
CASRN -- 68631-49-2

Benzene, 1,1'-oxybis(2,4,5-tribromo)-
2,2',4,4',5,5'-Hexabromodiphenyl ether
PBDE 153
BDE-153