



EPA/635/R-23/056a  
External Review Draft  
[www.epa.gov/iris](http://www.epa.gov/iris)

## **IRIS Toxicological Review of Perfluorodecanoic Acid [PFDA, CASRN 335-76-2] and Related Salts**

*April 2023*

Integrated Risk Information System  
Center for Public Health and Environmental Assessment  
Office of Research and Development  
U.S. Environmental Protection Agency  
Washington, DC

## ***Toxicological Review of Perfluorodecanoic Acid and Related Salts***

### **DISCLAIMER**

This document is an external review draft for review purposes only. This information is distributed solely for the purpose of predissemination peer review under applicable information quality guidelines. It has not been formally disseminated by EPA. It does not represent and should not be construed to represent any Agency determination or policy. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

# CONTENTS

AUTHORS   CONTRIBUTORS   REVIEWERS.....	xii
EXECUTIVE SUMMARY .....	xv
1. OVERVIEW OF BACKGROUND INFORMATION AND ASSESSEMENT METHODS .....	1-1
1.1. BACKGROUND INFORMATION ON PERFLUORODECANOIC ACID (PFDA) .....	1-1
1.1.1. Physical and Chemical Properties.....	1-1
1.1.2. Sources, Production, and Use.....	1-2
1.1.3. Environmental Fate and Transport .....	1-2
1.1.4. Potential for Human Exposure, including Populations and Lifestyles with Potentially Greater Exposure .....	1-3
1.2. SUMMARY OF ASSESSMENT METHODS .....	1-7
1.2.1. Literature Search and Screening .....	1-7
1.2.2. Evaluation of Individual Studies .....	1-10
1.2.3. Additional Epidemiology Considerations .....	1-11
1.2.4. Data Extraction .....	1-12
1.2.5. Evidence Synthesis and Integration .....	1-13
1.2.6. Dose-Response Analysis .....	1-14
2. LITERATURE SEARCH RESULTS.....	2-1
2.1. LITERATURE SEARCH AND SCREENING RESULTS .....	2-1
2.2. SUMMARY OF STUDIES MEETING PECO CRITERIA .....	2-2
3. PHARMACOKINETICS, EVIDENCE SYNTHESIS, AND INTEGRATION.....	3-1
3.1. PHARMACOKINETICS .....	3-1
3.1.1. Absorption.....	3-2
3.1.2. Distribution.....	3-3
3.1.3. Metabolism.....	3-12
3.1.4. Excretion.....	3-12
3.1.5. Summary of pharmacokinetic parameters.....	3-18
3.1.6. Evaluation of PBPK and PK Modeling .....	3-19
3.1.7. Approach for pharmacokinetic extrapolation of PFDA among rats, mice, and humans.....	3-22
3.2. NONCANCER HEALTH EFFECTS .....	3-25

***Toxicological Review of Perfluorodecanoic Acid and Related Salts***

3.2.1. HEPATIC EFFECTS..... 3-25

3.2.2. IMMUNE EFFECTS..... 3-54

3.2.3. DEVELOPMENTAL EFFECTS..... 3-98

3.2.4. MALE REPRODUCTIVE EFFECTS ..... 3-166

3.2.5. FEMALE REPRODUCTIVE EFFECTS ..... 3-190

3.2.6. CARDIOMETABOLIC EFFECTS..... 3-209

3.2.7. NEURODEVELOPMENTAL EFFECTS..... 3-240

3.2.8. ENDOCRINE EFFECTS ..... 3-247

3.2.9. URINARY EFFECTS ..... 3-269

3.2.10. GENERAL TOXICITY ..... 3-282

3.2.11. OTHER HEALTH EFFECTS..... 3-287

3.3. CARCINOGENICITY ..... 3-288

    3.3.1. CANCER..... 3-288

4. SUMMARY OF HAZARD IDENTIFICATION CONCLUSIONS..... 4-1

    4.1. SUMMARY OF CONCLUSIONS FOR NONCANCER HEALTH EFFECTS ..... 4-1

    4.2. SUMMARY OF CONCLUSIONS FOR CARCINOGENICITY..... 4-5

    4.3. CONCLUSIONS REGARDING SUSCEPTIBLE POPULATIONS AND LIFE STAGES ..... 4-5

5. DERIVATION OF TOXICITY VALUES ..... 5-1

    5.1. NONCANCER AND CANCER HEALTH EFFECT CATEGORIES CONSIDERED ..... 5-1

    5.2. NONCANCER TOXICITY VALUES ..... 5-1

        5.2.1. Oral Reference Dose (RfD) Derivation..... 5-2

        5.2.2. Selection of Lifetime Toxicity Value(s) ..... 5-25

        5.2.3. Subchronic Toxicity Values for Oral Exposure (Subchronic Oral Reference Dose [RfD]) Derivation..... 5-29

        5.2.4. Inhalation Reference Concentration (RfC) Derivation ..... 5-41

    5.3. CANCER TOXICITY VALUES ..... 5-42

REFERENCES..... R-1

SUPPLEMENTAL INFORMATION (see Volume 2)

## TABLES

Table 1-1. Physical-chemical properties of PFDA and related salts.....	1-1
Table 1-2. Serum PFDA concentrations based on NHANES 2013–2014 data (µg/L) .....	1-4
Table 1-3. PFDA levels at 10 military installations .....	1-6
Table 1-4. Populations, exposures, comparators, and outcomes (PECO) criteria .....	1-9
Table 2-1. Animal toxicity studies examining health effects after PFDA administration .....	2-3
Table 3-1. Volume of distribution values reported for animal studies.....	3-6
Table 3-2. PFDA total clearance in rats and mice .....	3-13
Table 3-3. Rat, mouse, and human pharmacokinetic parameters. ....	3-18
Table 3-4. DDEF calculations.....	3-23
Table 3-5. Associations between PFDA and serum biomarkers of hepatic function in <i>medium</i> confidence epidemiology studies .....	3-29
Table 3-6. Incidence and severity of hepatocyte lesions in S-D rats exposed to PFDA in 28-day gavage studies.....	3-34
Table 3-7. Percent change relative to controls in hepatocellular serum markers in short-term animal studies after PFDA exposure.....	3-37
Table 3-8. Percent change relative to controls in hepatobiliary serum markers in a 28-day rat study after PFDA exposure (NTP, 2018) .....	3-37
Table 3-9. Percent change relative to controls in serum proteins in a 28-day rat study after PFDA exposure (NTP, 2018).....	3-39
Table 3-10. Percent change relative to controls in liver weight (relative to body weight) due to PFDA exposure in short-term oral toxicity studies .....	3-42
Table 3-11. Evidence profile table for PFDA exposure and liver effects.....	3-51
Table 3-12. Summary of PFDA exposure and selected data on antibody response in humans .....	3-58
Table 3-13. Studies on PFDA and infectious disease in humans.....	3-62
Table 3-14. Studies on PFDA and hypersensitivity-related outcomes in humans .....	3-69
Table 3-15. Summary of PFDA and selected data on hypersensitivity in humans .....	3-70
Table 3-16. Percent change relative to controls in absolute spleen cell population counts in female B6C3F1/N mice exposed to PFDA exposure for 28-days (Frawley et al., 2018) .....	3-78
Table 3-17. Percent change relative to controls in blood leukocyte counts in female S-D rats exposed to PFDA exposure for 28-days (NTP, 2018) .....	3-81
Table 3-18. Percent change relative to controls in immune organ weights in short-term animal studies after exposure to PFDA .....	3-86
Table 3-19. Evidence profile table for PFDA exposure and immune effects .....	3-94
Table 3-20. Summary of 33 studies (from 35 publications) of PFDA exposure in relation to fetal and postnatal growth restriction measures sorted by overall confidence.....	3-123
Table 3-21. Summary of 12 studies of PFDA exposure and gestational duration measures.....	3-146
Table 3-22. Associations between PFDA and spontaneous abortion in epidemiology studies.....	3-150
Table 3-23. Percent changes relative to controls in fetal body weight in a developmental mouse study after PFDA exposure (Harris and Birnbaum, 1989).....	3-153
Table 3-24. Evidence profile table for PFDA exposure and developmental effects .....	3-159
Table 3-25. Associations between serum PFDA and semen parameters in epidemiology studies .....	3-167
Table 3-26. Evidence profile table for PFDA exposure and male reproductive effects.....	3-186
Table 3-27. Associations between PFDA and time to pregnancy in epidemiology studies .....	3-194