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Provisional Peer-Reviewed Toxicity Values for

Fluorene
(CASRN 86-73-7)

U.S. EPA Office of Research and Development
Center for Public Health and Environmental Assessment

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Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA Office of Research and Development (ORD) Center for Public Health and Environmental Assessment (CPHEA) website at https://ecomments.epa.gov/pprtv.

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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AR	androgen receptor
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMC	benchmark concentration
BMCL	benchmark concentration lower confidence limit
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service registry number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPHEA	Center for Public Health and Environmental Assessment
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-*S*-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	*N*-acetyl-β-D-glucosaminidase
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand White (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure-activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase, also known as AST
SGPT	serum glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_C	composite uncertainty factor
UF_D	database uncertainty factor
UF_H	intraspecies uncertainty factor
UF_L	LOAEL-to-NOAEL uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
U.S.	United States of America
WBC	white blood cell

Abbreviations and acronyms not listed on this page are defined upon first use in the PPRTV assessment.

DRAFT PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR FLUORENE (CASRN 86-73-7) [Noncancer Values]

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund program. PPRTVs are derived after a review of the relevant scientific literature using established U.S. Environmental Protection Agency (U.S. EPA) guidance on human health toxicity value derivations.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

Currently available PPRTV assessments can be accessed on the U.S. EPA's PPRTV website at https://www.epa.gov/pprtv. PPRTV assessments are eligible to be updated on a 5-year cycle and revised as appropriate to incorporate new data or methodologies that might impact the toxicity values or affect the characterization of the chemical's potential for causing toxicologically relevant human-health effects. Questions regarding nomination of chemicals for update can be sent to the appropriate U.S. EPA eComments Chemical Safety website at https://ecomments.epa.gov/chemicalsafety/.

QUALITY ASSURANCE

This work was conducted under the U.S. EPA Quality Assurance (QA) program to ensure data are of known and acceptable quality to support their intended use. Surveillance of the work by the assessment managers and programmatic scientific leads ensured adherence to QA processes and criteria, as well as quick and effective resolution of any problems. The QA manager, assessment managers, and programmatic scientific leads have determined under the QA program that this work meets all U.S. EPA quality requirements. This PPRTV assessment was written with guidance from the CPHEA Program Quality Assurance Project Plan (PQAPP), the QAPP titled *Program Quality Assurance Project Plan (PQAPP) for the Provisional Peer-Reviewed Toxicity Values (PPRTVs) and Related Assessments/Documents (L-CPAD-0032718-QP)*, and the PPRTV assessment development contractor QAPP titled *Quality Assurance Project Plan—Preparation of Provisional Toxicity Value (PTV) Documents (L-CPAD-0031971-QP)*. As part of the QA system, a quality product review is done prior to management clearance. A Technical Systems Audit may be performed at the discretion of the QA staff.

All PPRTV assessments receive internal peer review by at least two CPHEA scientists and an independent external peer review by at least three scientific experts. The reviews focus on whether all studies have been correctly selected, interpreted, and adequately described for the purposes of deriving a provisional reference value. The reviews also cover quantitative and qualitative aspects of the provisional value development and address whether uncertainties associated with the assessment have been adequately characterized.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the toxicologically relevant effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. EPA programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVS

Questions regarding the content of this PPRTV assessment should be directed to the U.S. EPA ORD CPHEA website at https://ecomments.epa.gov/pprtv.

1. INTRODUCTION

Fluorene is a discrete organic chemical and a member of the polycyclic aromatic hydrocarbon (PAH) class of chemicals. Fluorene is a component of petroleum (NCBI, 2021). It is used as an intermediate for pesticides and dyes (NCBI, 2021). Fluorene is listed as active in commerce on the Toxic Substances Control Act (TSCA) public inventory (U.S. EPA, 2021c) and is registered with Europe's Registration, Evaluation, Authorization, and Restriction of Chemicals (REACH) program (ECHA, 2021).

The 2006 Inventory Updating Reporting (IUR Rule), a precursor to the U.S. EPA's Chemical Data Reporting (CDR) database, reported that the aggregate volume of fluorene produced and imported in the United States was <500,000 pounds in 2005 (U.S. EPA, 2021a). Its use was reported as "other" for commercial and consumer purposes; industrial use is reported as a fuel (U.S. EPA, 2021a). More recent data were not available. Fluorene can be isolated from coal tar by distillation and recrystallization of the fluorene fraction, or by continuous countercurrent crystallization from higher fluorene fractions (Schmidt et al., 2015). A patented synthetic route describes passing 2-methylbiphenyl over a palladium-charcoal catalyst at 400−500°C, forming fluorene through cyclodehydrogenation (Orchin, 1947).

The empirical formula for fluorene is $C_{13}H_{10}$ and its structure is shown in Figure 1. Table 1 summarizes the physicochemical properties for fluorene. Experimental property data were selected preferentially over estimated property data. In the absence of experimental data, estimated values from the U.S. EPA's CompTox Chemicals Dashboard were reported and indicated with a footnote. Based on the reported vapor pressure, fluorene will exist primarily in the vapor phase if released to the atmosphere. Fluorene is moderately volatile from water and moist soil surfaces based on its Henry's law constant; however, the soil adsorption coefficient indicates that fluorene will strongly sorb to soil and sediment, potentially limiting volatilization from these surfaces. Due to strong sorption to soil and low water solubility, the potential to leach to groundwater or undergo runoff after precipitation is low.

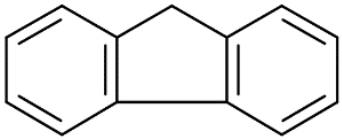


Figure 1. Fluorene (CASRN 86-73-7) Structure

Table 1. Physicochemical Properties of Fluorene (CASRN 86-73-7)

Property (unit)	Value[a]
Physical state	Solid
Boiling point (°C)	295
Melting point (°C)	115
Density (g/cm^3)	1.10 (predicted average)
Vapor pressure (mm Hg at 25°C)	6.00×10^{-4}
pH (unitless)	NA
Acid dissociation constant (pKa) (unitless)	NA
Solubility in water (mol/L)	1.15×10^{-5}
Octanol-water partition coefficient (log K_{ow})	4.18
Henry's law constant (atm-m^3/mole)	9.62×10^{-5}
Soil adsorption coefficient (L/kg)	5.01×10^{3}
Atmospheric OH rate constant (cm^3/molecule-sec)	1.32×10^{-11}
Relative vapor density (air = 1)	NA (solid)
Molecular weight (g/mol)	166.223
Flash point (°C)	126 (predicted average)

[a]Data were extracted from the U.S. EPA CompTox Chemicals Dashboard (fluorene, CASRN 86-73-3; https://comptox.epa.gov/dashboard/dsstoxdb/results?search=DTXSID8024105; accessed August 4, 2022) (U.S. EPA, 2021b). All values are experimental averages unless otherwise specified.

NA = not applicable.

A summary of available toxicity values for fluorene from the U.S. EPA and other agencies/organizations is provided in Table 2. Reference values are based on chronic exposure unless otherwise indicated.

Table 2. Summary of Available Toxicity Values and Qualitative Conclusions Regarding Carcinogenicity for Fluorene (CASRN 86-73-7)

Source/Parameter[a,b]	Value (applicability)	Notes	Reference[c]
Noncancer			
IRIS (RfD)	0.04 mg/kg-d	Based on decreased RBC count, packed blood cell volume, and hemoglobin concentration in a 13-wk mouse gavage study	U.S. EPA (1990)
HEAST (sRfD)	0.4 mg/kg-d	Based on decreased RBC count in a 13-wk mouse gavage study	U.S. EPA (2011b)
DWSHA (RfD)	0.04 mg/kg-d	Based on a NOAEL for hematological effects in mice	U.S. EPA (2018); U.S. EPA (1991)
ATSDR (intermediate oral MRL)	0.4 mg/kg-d	Based on increased relative liver weight in a 90-d mouse gavage study	ATSDR (1995)
IPCS	NV	NA	IPCS (1998)
CalEPA	NV	NA	CalEPA (2021); CalEPA (2020)
OSHA	NV	NA	OSHA (2021a); OSHA (2021b); OSHA (2021c)
NIOSH	NV	NA	NIOSH (2018)
ACGIH	NV	NA	ACGIH (2020)
DOE (PAC)	PAC-1: 6.6 mg/m^3 PAC-2: 72 mg/m^3 PAC-3: 430 mg/m^3	PAC-1 and PAC-2 based on TEELs; PAC-3 based on mouse i.p. LD_{50}	DOE (2018)
USAPHC (air-MEG)	1-h critical: 500 mg/m^3 1-h marginal: 150 mg/m^3 1-h negligible: 25 mg/m^3	Based on TEELs	U.S. APHC (2013)
USAPHC (water-MEG)	1-yr negligible: 5.6 mg/L	5 L intake rate; based on IRIS subchronic noncancer study	U.S. APHC (2013)
USAPHC (soil-MEG)	1-yr negligible: 5,200 mg/kg	Developed by USAPHC outside the standard methodology	U.S. APHC (2013)
Cancer			
IRIS (WOE)	Group D, not classifiable as to human carcinogenicity	Based on no human data and inadequate data from animal bioassays	U.S. EPA (1990)
PPRTV (cancer OSF)	NV	NA	U.S. EPA (2002a)
HEAST	NV	NA	U.S. EPA (2011b)
DWSHA	D, not classifiable as to human carcinogenicity	NA	U.S. EPA (2018)
NTP	NV	NA	NTP (2016)
IARC	Group 3, not classifiable as to its carcinogenicity to humans	Available studies in experimental animals were considered inadequate to permit evaluation	IARC (2010)

Table 2. Summary of Available Toxicity Values and Qualitative Conclusions Regarding Carcinogenicity for Fluorene (CASRN 86-73-7)

Source/Parameter[a,b]	Value (applicability)	Notes	Reference[c]
CalEPA	NV	NA	CalEPA (2021), CalEPA (2020)
ACGIH	NV	NA	ACGIH (2020)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Registry; CalEPA = California Environmental Protection Agency; DOE = U.S. Department of Energy; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; IARC = International Agency for Research on Cancer; IPCS = International Programme on Chemical Safety; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; PPRTV = Provisional Peer-Reviewed Toxicity Value; USAPHC = U.S Army Public Health Command.
[b]Parameters: MEG = military exposure guideline; MRL = minimum risk level; OSF = oral slope factor; PAC = protective action criteria; RfD = reference dose; sRfD = subchronic reference dose; WOE = weight of evidence.
[c]Reference date is the publication date for the database and not the date the source was accessed.

i.p. = intraperitoneal; LD_{50} = median lethal dose; NA = not applicable; NOAEL = no-observed-adverse-effect level; NV = not available; RBC = red blood cell; TEEL = Temporary Emergency Exposure Limit.

Literature searches were conducted in June 2019 and updated most recently in July 2023 for studies relevant to the derivation of provisional toxicity values for fluorene. Searches were conducted using the U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, TOXLINE[1] (including TSCATS1), Scopus, and Web of Science. The National Technical Reports Library (NTRL) was searched for government reports from 2018 through September 2020[2]. The following resources were searched outside of HERO for health-related values: American Conference of Governmental Industrial Hygienists (ACGIH), Agency for Toxic Substances and Disease Registry (ATSDR), California Environmental Protection Agency (CalEPA), Defense Technical Information Center (DTIC), European Centre for Ecotoxicology and Toxicology of Chemicals (ECETOC), European Chemicals Agency (ECHA), the U.S. EPA Chemical Data Access Tool (CDAT), the U.S. EPA ChemView, the U.S. EPA Integrated Risk Information System (IRIS), the U.S. EPA Health Effects Assessment Summary Tables (HEAST), the U.S. EPA Office of Water (OW), International Agency for Research on Cancer (IARC), the U.S. EPA TSCATS2/TSCATS8e, the U.S. EPA High Production Volume (HPV), Chemicals via International Programme on Chemical Safety (IPCS) INCHEM, Japan Existing Chemical Data Base (JECDB), Organisation for Economic Co-operation and Development (OECD) Screening Information Data Sets (SIDS), OECD International Uniform Chemical Information Database (IUCLID), OECD HPV, National Institute for Occupational Safety and Health (NIOSH),

[1]Note that this version of TOXLINE is no longer updated (https://www.nlm.nih.gov/databases/download/toxlinesubset.html); therefore, it was not included in the literature search update from July 2023.
[2]NTRL was a subset of TOXLINE until December 2019 when TOXLINE was discontinued. Searches of NTRL were conducted starting in 2018 to ensure that references were not missed due to delays in importing items into the database.

National Toxicology Program (NTP), Occupational Safety and Health Administration (OSHA), and World Health Organization (WHO).

2. REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER ONLY)

Table 3 provides an overview of the relevant noncancer evidence base for fluorene and includes all potentially relevant repeated-dose, short-term-, subchronic-, and chronic studies, as well as reproductive and developmental toxicity studies. Principal studies used in the PPRTV assessment are identified in bold. The phrase "statistical significance" and term "significant," used throughout the document, indicates a *p*-value of < 0.05 unless otherwise specified.

Table 3. Summary of Potentially Relevant Noncancer Data for Fluorene (CASRN 86-73-7)

Category[a]	Number of Male/Female, Strain Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
Human							
			1. Oral (mg/kg-d)				
ND							
			2. Inhalation (mg/m^3)				
ND							
Animal							
			1. Oral (mg/kg-d)				
Short-term	ND						
Subchronic	**8 M/0 F, Wistar rat, gavage, 60 d**	**0, 1, 10, 100**	**Increased relative liver weight.**	**1**	**10**	**Peiffer et al. (2016)**	**PS, PR**
Subchronic	20 M/20 F, Crl:CD-1 mouse, gavage, 13 wk	0, 125, 250, 500	Decreased RBC count, packed cell volume, and hemoglobin; increased serum total bilirubin and cholesterol and decreased BUN; increased absolute and relative liver and spleen weights; increased incidences of centrilobular cytomegaly, cytoplasmic alteration, and pigmentation of Kupffer cells in the liver (males only), and hemosiderosis and hematopoietic cell proliferation in the spleen (both sexes).	125	250	TRL (1989)	NPR, IRIS
Chronic	ND						
Reproductive/ Developmental	ND						

Table 3. Summary of Potentially Relevant Noncancer Data for Fluorene (CASRN 86-73-7)

Category[a]	Number of Male/Female, Strain Species, Study Type, Reported Doses, Study Duration	Dosimetry[b]	Critical Effects	NOAEL[b]	LOAEL[b]	Reference (comments)	Notes[c]
2. Inhalation (mg/m^3)							
Short-term	18 M/0 F, Wistar Han rat, nose-only vapor inhalation, 6 h/d, 7 d/wk, 2 wk	0, 0.003, 0.3	No toxicologically relevant effects on behavior were observed.	0.3	NDr	Peiffer et al. (2013) (Other than behavior, no toxicological endpoints were evaluated in fluorene-exposed rats.)	PR
Subchronic	ND						
Chronic	ND						
Reproductive/ Developmental	ND						

[a]Duration categories are defined as follows: Acute = exposure for ≤24 hours; short-term = repeated exposure for 24 hours to ≤30 days; long-term (subchronic) = repeated exposure for >30 days or ≤10% life span for humans (>30 days up to approximately 90 days in typically used laboratory animal species); and chronic = repeated exposure for >10% life span for humans (>~90 days to 2 years in typically used laboratory animal species) (U.S. EPA, 2002b).
[b]Dosimetry: Doses are presented as ADDs (mg/kg-day) for oral noncancer effects and as HECs (in mg/m^3) for inhalation noncancer effects. The HEC from animal studies was calculated using the equation for extrarespiratory effects from a Category 3 Gas (U.S. EPA, 1994): HEC_{ER} = continuous concentration in mg/m^3 × ratio of animal:human blood gas partition coefficients (default value of 1 applied).
[c]Notes: Used by the IRIS program to derive a chronic oral RfD (U.S. EPA, 1990); NPR = not peer reviewed; PR = peer reviewed; PS = principal study.

ADD = adjusted daily dose; BUN = blood urea nitrogen; ER= extrarespiratory; F = female(s); HEC = human equivalent concentration; IRIS = Integrated Risk Information System; LOAEL = lowest-observed-adverse-effect level; M = male(s); ND = no data; NDr = not determined; NOAEL = no-observed-adverse-effect level; RBC = red blood cell; RfD = reference dose.

2.1. HUMAN STUDIES

Select human studies that reported associations between biomarkers of exposure to fluorene and health effects are presented in Table 4 and briefly summarized below. In general, studies that reported human data were confounded by co-exposures to other PAHs and did not specify the route of exposure (i.e., oral, inhalation, and other routes were likely in all cases.) Although quantitative biomonitoring data were reported, information does not exist to support the calculation of direct fluorene exposure (i.e., external dose) from reported exposure biomarker concentrations (i.e., physiologically based pharmacokinetic [PBPK] models were not identified for fluorene). For these reasons, no human studies were considered suitable for quantitative dose-response analysis, and no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) values were not identified.

Monitoring levels of the mono-hydroxylated fluorene metabolites, 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene, is a common proxy used for estimating fluorene exposure in humans (Gmeiner et al., 2002; Grantham, 1963; Dewhurst, 1962; Neish, 1948). Nearly all available studies evaluated associations between estimated fluorene exposure (based on urinary or blood plasma levels of fluorene or the mono-hydroxylated metabolites) and health outcomes (or biomarkers of health outcomes). Numerous studies reported associations between exposure to fluorene from PAH mixtures and a variety of negative health outcomes for males and females, including reduced lung function (Peng et al., 2023; Alhamdow et al., 2021; Cakmak et al., 2017), reduced liver function in adults (Mallah et al., 2023), increased risk for cardiovascular disease in a population of adult petrochemical workers (SUNY, 2023), greater likelihood of risk factors for metabolic syndrome and dyslipidemia (Shahsavani et al., 2022; Guo et al., 2018b; Ranjbar et al., 2015), associations with markers of age-related diseases (Yang et al., 2023; Chen and Chen, 2022), increased inflammation in adolescents (Verheyen et al., 2021), increased biomarkers of oxidative stress in adults (Verheyen et al., 2021; Zhu et al., 2021), and obesity during childhood and/or adolescence (Liu et al., 2023; Dobraca et al., 2020; Uche et al., 2020) or adulthood (Wang et al., 2022; Ranjbar et al., 2015). There are also many studies that found sex-specific effects of fluorene due to the nature of the endpoint evaluated (e.g., sperm effects observed in males) or that reported results stratified by sex in which only one sex was found to be negatively affected by exposure. In males, fluorene exposure has been linked to deleterious sperm effects (Chen et al., 2021; Yang et al., 2017; Han et al., 2011). Exposure in females has been associated with oxidative stress in pregnant mothers working outside the home (Lou et al., 2019), negative effects on parameters of liver function (Xu et al., 2021), delays in breast developments (without effect on the age at pubertal transition) (Dobraca et al., 2020), and increases in all-cause (noncancer) mortality (Chen et al., 2020). A few studies found evidence for a relationship between fluorene exposure and negative health outcomes but the results were not statistically significant; these include increases in serum biomarkers of cardiovascular disease (Clark et al., 2012), presence of esophageal squamous dysplasia (Mwachiro et al., 2021), risk for preterm labor (Agarwal et al., 2017), risk of osteoporosis and decreased bone density (Guo et al., 2018a), and risk of low-birth-weight offspring (Kumar et al., 2020).

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Mortality				
Chen et al. (2020) **(United States)** Cross-sectional study of 1,409 subjects (692 males and 717 females aged ≥20 yr) from NHANES (2001−2006).	Based on urinary levels of 2-OH fluorene and 3-OH fluorene.	Mortality outcomes were evaluated from the National Death Index (linked to death certificate data).	No significant association was found between levels of 2-OH fluorene or 3-OH fluorene and cardiovascular or cancer mortality. In females only, levels of 3-OH fluorene were significantly associated with an increased risk of all-cause mortality (HR = 2.2, 95% CI = [1.2, 3.8]).	Environmental exposure to fluorene in adults was associated with noncarcinogenic mortality, as also found for some of the other PAHs evaluated.
Cardiovascular effects				
Clark et al. (2012) **(United States)** Cross-sectional study of 3,219 subjects (1,547 males and 1,672 females aged ≥20 yr) from NHANES (2001−2004).	Based on urinary levels of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	Serum biomarkers of cardiovascular disease (fibrinogen, homocysteine, and WBC counts) were measured.	Though not significant, an interquartile increase in level (75^{th} vs. 25^{th} percentile) for each fluorene metabolite was positively associated with measurements of cardiovascular disease in nonsmoking subjects.	There was not strong evidence for a relationship between PAH exposure (including fluorene) and markers of cardiovascular disease after controlling for tobacco use.
Guo et al. (2018b) **(China)** Cross-sectional study of 2,476 subjects, *n* = 1,884 (675 males and 1,209 females, mean age = 51.6 yr) without metabolic syndrome (MetS) and *n* = 592 (193 males and 399 females, mean age = 57.7 yr) with MetS from the Wuhan-Zhuhai cohort.	Based on the summed urinary levels of 2-OH fluorene and 9-OH fluorene.	Heart rate variability indices (including very low frequency [VLF], low frequency [LF], high frequency [HF], and total power [TP]) were measured.	High levels of fluorene metabolites were significantly associated with decreased VLF, LF, and TP in subjects with MetS (graphs representing 95% CI of OR for highest tertile vs. reference do not include zero for these indices). There were no significant associations in subjects without MetS.	The association between PAH exposure (including fluorene) and heart rate variability differed by MetS status.
SUNY (2023) **(China)** Cross-sectional study of 746 (601 males and 145 females, median age = 49 yr) petrochemical workers from two different plants in the largest industrial petroleum and petrochemical production region in China.	Based on the summed urinary levels of 2-OH fluorene and 3-OH fluorene.	Cardiovascular measurements of hypertension (including systolic blood pressure, diastolic blood pressure, cardiac frequency, and pulse rate) were obtained.	The summed fluorine metabolites were significantly associated with increases in systolic blood pressure (*r* = 0,151), diastolic blood pressure (*r* = 0.139), and cardiac frequency (*r* = 0.121).	PAH exposure (including fluorene) was associated with increased risk of hypertension in a population of petrochemical workers.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Liver effects				
Mallah et al. (2023) **(United States)** Cross-sectional study of 2,515 subjects aged ≥18 yr (1,211 males, 1,304 females, mean age = 45.71 yr) from NHANES (2003−2016).	Based on urinary levels of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	Liver function indices (ALT, AST, GGT, LDH, and total bilirubin) and blood lipid levels (TG, LDL-C, HDL-C, and TC) were measured.	There were significant positive relationships between each metabolite and GGT: 2-OH fluorene (OR = 1.61, 95% CI = [1.23, 2.11]), 3-OH fluorene (OR = 1.54, 95% CI = [1.21, 1.95]), and 9-OH fluorene (OR = 2.11, 95% CI = [1.52, 2.95]).	PAH exposure (including fluorene) was negatively associated with liver function in adults.
Xu et al. (2021) **(United States)** Cross-sectional analysis of 3,194 adolescents (1,648 males, mean age = 15.5 yr; 1,546 females, mean age = 15.4 yr) from NHANES (2003−2016).	Based on levels of 2-OH fluorene and 3-OH fluorene.	Liver function indices (ALT, AST, GGT), inflammation markers (C-reactive protein and WBC count), and indicators of blood lipid levels (TG, LDL-C, HDL-C, and TC; log 10-transformed for analysis) were measured.	In females, 2-OH fluorene was significantly associated with interquartile increases in % change ($\Delta_{\%}$) for ALT ($\Delta_{\%}$ = 5.07, 95% CI = [1.83, 8.29]), WBC count ($\Delta_{\%}$ = 3.56, 95% CI = [1.21, 5.96]), TG levels ($\Delta_{\%}$ = 6.99, 95% CI = [0.73, 13.64]), and TC levels ($\Delta_{\%}$ = 1.70, 95% CI = [0.12, 3.31[). There were no significant associations among males for either fluorene metabolite.	PAH exposure (including fluorene) was negatively associated with liver function in female adolescents.
Respiratory effects				
Alhamdow et al. (2021) **(Sweden)** Cross-sectional study using data from a subset (*n* = 1,000, median age = 22.6 yr) of 2,223 subjects from the Barn/Child, Allergy, Milieu, Stockholm, Epidemiology cohort.	Based on the summed urinary levels of 2-OH fluorene and 3-OH fluorene.	Measurements of respiratory function (FEV_1, FVC) were obtained via standard practice and fractional exhaled nitric oxide concentration (FeNo) was measured as a biomarker for eosinophilic pulmonary inflammation.	There were significant inverse relationships between summed fluorene metabolites and FEV_1 (β = −73, 95% CI = [−115, −30]) as well as FVC (β = −59, 95% CI = [−111, −6.5]).	Low-level exposure to PAHs (including fluorene) was associated with reduced lung function in young adults.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Cakmak et al. (2017) **(Canada)** Cross-sectional study of 3,531 subjects from the Canadian Health Measures Survey cycles 2 (2009−2011) and 3 (2012−2013), aged 6−79 yr.	Based on individual and summed urinary levels of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	Measurements of respiratory function (FEV_1, FVC) were obtained via standard practice.	All fluorene metabolites were significantly associated with interquartile increases in % change for FEV_1 and FVC with combined levels reaching the highest level of magnitude (FEV_1: $\Delta_{\%} = -1.41$, 95% CI = [−2.68, −0.14]; FVC: $\Delta_{\%} = -1.28$, 95% CI = [−2.46, −0.10]).	Exposure to PAHs (including fluorene) may negatively impact lung function.
Peng et al. (2023) **(United States)** Cross-sectional study of 3,015 subjects (500 individuals with incidence of COPD and 2,015 without incidence of COPD) aged 20−79 yr from NHANES (2007−2016).	Based on individual and summed urinary levels of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	Diagnostic criteria for COPD were based on cutoffs for measurements of respiratory function (FEV_1/FVC <70%) obtained following inhaled beta2-adrenergic bronchodilator medication for individuals in study yr 2007−2012 and self-reports of an affirmative response to the question "Have you ever been told that you have COPD" for individuals in study yr 2013−2017.	Increasing levels of urinary biomarkers for fluorene exposure were significantly and positively associated with risk for diagnosis of COPD in 2-OH fluorene (OR = 2.29. 95% CI = [1.42, 3.68] for tertile 3) and 9-OH (OR = 1.72, 95% CI = [1.04, 2.84] for tertile 2). Summed levels of fluorene metabolites were significantly associated with COPD for the highest tertile of exposure (OR = 2.74, 95% CI = [1.77, 4.23]).	Exposure to PAHs (including fluorene) was associated with risk for a positive diagnosis of COPD.
Pregnancy outcomes				
Agarwal et al. (2017) **(India)** Case-control study of 84 healthy, pregnant women recruited from a medical college; controls (*n* = 55) included gestational age >36 wk (full-term delivery) undergoing spontaneous labor at term; cases (*n* = 29) included gestational age <36 wk (preterm delivery) undergoing preterm labor.	Based on fluorene levels in placental tissue samples.	Levels of MDA and GSH were measured in placental tissue samples as biomarkers of redox status.	Though not significant, higher levels of fluorene (placental levels; µg/L) were observed in women with full-term deliveries (controls; mean = 0.012, SD = 0.06) compared to women with preterm deliveries (cases; mean = 0.0007, SD = 003).	Observations of increased MDA and decreased GSH in cases relative to controls suggest a possible role for PAHs (other than fluorene) in early delivery.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Kumar et al. (2020) **(India)** Case-control study of 175 pregnant women recruited from a medical college; controls (n = 120, mean age = 23.7 yr) with normal-birth-weight offspring; cases (n = 55, mean age = 22.3 yr) with low-birth-weight offspring.	Based on fluorene levels in maternal blood (placental and cord blood levels of fluorene were not used due to low detection rates).	Birth weights were measured and evaluated (low vs. normal).	Fluorene exposure above the median level as measured in maternal blood was associated with an increased likelihood of low-birth-weight offspring (OR = 9.36, 95% CI = [0.50, 175.04], p = 0.135).	The blood concentrations of some PAHs (including fluorene) were associated with low-birth-weight offspring.
Lou et al. (2019) **(China)** Cross-sectional study of 188 pregnant women (mean age = 29.2 yr) randomly recruited during regular pregnancy checks; cases (n = 138) with pregnant women working outside the home and controls (n = 24) with pregnant women not working outside the home.	Based on urinary levels of 2-OH fluorene.	Urinary levels of 8-OHdG, as a biomarker of DNA oxidative damage, were measured.	2-OH fluorene was significantly (r = 0.496; p < 0.01) associated with urinary 8-OHdG in pregnant women working outside the home. No significant associations were found in pregnant women not working outside the home.	Exposure to some PAHs (including fluorene) was associated with oxidative stress in pregnant women who worked in jobs outside the home.
Sperm parameters				
Chen et al. (2021) **(China)** Cross-sectional analysis (n = 656) based on subjects from the Male Reproductive Health in Chongqing College Students cohort study with data available at baseline (2013) and 1-yr follow-up (2014); average age at baseline = 20 yr.	Based on individual urinary levels of 2-OH fluorene as well as fluorene levels measured via PM2.5 sampling.	Sperm parameters (sperm concentration, progressive motility [%], normal morphology [%], and sperm DNA integrity, fragmentation, and stainability via sperm chromatin structural assay) and serum biomarkers for reproductive health (estradiol, FSH, LH, prolactin, progesterone, and testosterone) were measured.	2-OH fluorene was significantly negatively associated with sperm progressive motility (β = −4.347, 95% CI = [−7.628, −0.949]) and serum progesterone levels (β = −7.877, 95% CI = [−14.137, −1.162]). Fluorene exposure as measured via PM2.5 sampling was positively associated with serum estradiol (estimates not reported) and inversely associated with LH (β = −13.9, 95% CI = [−18.5, −8.9]), prolactin (β = −100.0, 95% CI = [−100.0, −100.0]), and testosterone (β = −15.6, 95% CI = [−21.9, −8.9]).	Environmental exposure to PAHs (including fluorene) was negatively associated with male reproductive function.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Han et al. (2011) **(China)** Cross-sectional study of 232 subjects from the general male population (mean age = 31.89 yr) assessed in December 2007.	Based on urinary levels of 2-OH fluorene.	Semen quality, sperm apoptotic markers (Annexin V assay), and sperm DNA damage (comet assay) were evaluated.	2-OH fluorene was significantly negatively associated with Annexin V^-/PI^- spermatozoa (living cells without PS translocation) (β = −11.10, 95% CI = [−17.31, −4.88]) and positively associated with PI^+ (necrotic) cells (β = 8.91, 95% CI = [2.99, 14.84]); it was also weakly associated with tail % (β = 5.04, 95% CI = [−0.99, 11.07]; $p = 0.07$).	Environmental exposure to PAHs (including fluorene) was associated with sperm DNA damage.
Yang et al. (2017) **(China)** Cross-sectional study of 793 male partners in subfertile couples (mean age = 32 yr) with sufficient unprocessed urine for analysis of PAH metabolites.	Based on urinary levels of 2-OH fluorene and 9-OH fluorene.	Sperm indices (sperm DNA damage via the comet assay and apoptosis via the Annexin V/PI assay) were measured.	9-OH fluorene was significantly positively associated with tail length and comet length (p values for trend = 0.05 and 0.01, respectively) and inversely associated with percentage of Annexin V^-/PI^-spermatozoa (i.e., living cells without PS translocation; $p < 0.10$).	Environmental exposure to PAHs (including fluorene) was associated with increased sperm DNA damage and apoptosis.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Obesity in children and adults (also timing of puberty)				
Dobraca et al. (2020) **(United States)** Cohort study of 404 girls (aged 6−8 yr at baseline, mean = 7.4 yr) enrolled in the Northern California site of the Breast Cancer and the Environment Research Program cohort.	Based on summed urinary levels of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	Adiposity (BMI and waist-to-height ratio) and pubertal onset according to the Tanner stages of breast and pubic hair development were evaluated from age 7 through 16 yr.	At baseline (approximately 7 yr): The highest tertiles of fluorene metabolites were associated with higher adiposity. Over the follow-up period (7−16 yr): High tertiles of fluorene metabolites were significantly associated with increased BMI (7.0 kg/m^2 increase at the high tertile compared to 6.0 kg/m^2 increase at the lowest tertile). The highest tertiles of fluorene metabolites were significantly associated with increased waist-to-height ratio. Breast development occurred significantly later at the highest tertiles of fluorene metabolites (10.3 yr) compared to the lowest tertile (9.9 yr) in normal-weight girls. A nonsignificant delay in pubic hair development was also observed in normal-weight girls with higher tertiles of fluorene metabolites.	Exposure to PAHs (including fluorene) during childhood may influence adiposity during adolescence and affect pubertal timing.
Liu et al. (2023) (**Canada, Iran, Korea, and United States**) Meta-Analysis of eight cross-sectional studies with a pooled sample size of 68,454 individuals (aged >3 yr in all studies).	Based on pooled effect estimates of urinary and blood levels of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	Obesity criteria were defined by the individual studies included in the meta-analysis.	9-OH fluorene was significantly positively associated with obesity after adjusting for physical activity (OR = 1.37, 95% CI = [1.11, 1.69]) and in subgroup analyses for individuals aged 3−19 yr (OR = 1.53, 95% CI = [1.20, 1.96]).	The association between PAH exposure (including fluorene) was positively associated with increased risk for obesity in children and adolescents.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Ranjbar et al. (2015) **(United States)** Cross-sectional study of 4,765 subjects (aged ≥20 yr) from NHANES (2001−2008). The mean ages of non-obese (*n* = 3,085) and obese (*n* = 1,680) subjects were 45.1 and 47.2 yr, respectively.	Based on urinary levels of 2-OH fluorene and 3-OH fluorene.	Obesity (based on BMI ≥30 kg/m^2), having three or more risk factors for metabolic syndrome (3RFMetS), type 2 diabetes, hypertension, and dyslipidemia were evaluated.	For both fluorene metabolites, the highest quintiles of exposure were significantly associated with a greater likelihood of 3RFMetS (2-OH fluorene: OR = 1.66, 95% CI = [1.05, 2.62]; 3-OH fluorene: OR = 1.80, 95% CI = [1.25, 2.59]) and dyslipidemia (2-OH fluorene: OR = 1.54, 95% CI = [1.20, 1.97]; 3-OH fluorene: OR = 1.57, 95% CI = [1.21, 2.05]).	Exposure to PAHs (including fluorene) was associated with obesity and obesity-related cardiometabolic health risk factors.
Shahsavani et al. (2022) **(Iran)** Cross-sectional analysis of 200 individuals (mean age = 40.2 yr).	Based on urinary levels of 2-OH fluorene.	Levels of biomarkers for lipid peroxidation (urinary MDA) and metabolic factors (blood serum FBS, LDL-C, HDL-C, TC, TG, and other blood biochemical parameters) were measured. Body measurements (weight, height, and waist circumference), blood pressure parameters, and MetS status were measured and/or evaluated by trained health professionals using standardized protocols.	2-OH fluorene was significantly associated with increased systolic blood pressure (r = 0.11), diastolic blood pressure (r = 0.92), TG level (r = 0.03), waist circumference (r = 0.16), and hemoglobin (r = 0.44).	Environmental exposure to PAHs (including fluorene) was related to an increase in risk for metabolism- and obesity-related health outcomes.
Uche et al. (2020) **(United States)** Cross-sectional study of 50,048 children and adolescents (aged 6−17 yr; mean age = 11.5 yr) from NHANES (1999−2016).	Based on various environmental factors, including urinary levels of 9-OH fluorene (not further specified).	Obesity was measured (BMI and waist-to-height ratio).	9-OH fluorene was significantly positively associated with obesity based on BMI (OR = 1.509, 95% CI = [1.230, 1.851]) and abdominal obesity (OR = 1.478, 95% CI = [1.182, 1.847]) in children/adolescents. Though not significant, females with higher levels of 9-OH fluorene were more likely than males to be obese.	Environmental factors (including exposure to fluorene and other PAHs) were associated with childhood obesity.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Wang et al. (2022) **(United States)** Cross-sectional study of 2,691 nonsmoking subjects (959 non-Hispanic white, 585 non-Hispanic black, and 767 Hispanic subjects aged ≥20 yr) from NHANES (2001−2016).	Based on urinary levels (individual and summed) of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	FM% of the trunk and legs was determined via dual-energy x-ray absorptiometry results, and body measurements (weight, height, and waist circumference) were obtained by trained health professionals using standardized protocols.	In the total population, 3-OH fluorene was significantly inversely correlated with multiple outcomes including total FM% (r = −0.07) and trunk FM% (r = −0.08), while 9-OH was significantly positively correlated with trunk FM% (r = 0.09), trunk/leg ratio (r = 0.10), and waist circumference (r = 0.08). In analyses stratified by race/ethnicity, 9-OH fluorene was significantly positively correlated with waist circumference (r = 0.18), trunk FM% (r = 0.22), trunk/leg ratio (r = 0.21), and total FM% (r = 0.20) in the non-Hispanic black population.	PAH exposure (including fluorene) was associated with increased risk for obesity-related health outcomes and the associations varied based on race/ethnicity.
Musculoskeletal effects				
Guo et al. (2018a) **(United States)** Cross-sectional study of 1,768 women (aged ≥20 yr) from NHANES (2005−2010).	Based on urinary levels of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	Bone mass density and osteoporosis were evaluated.	Compared with the first tertile, the third tertile of 2-OH fluorene in women was associated with significantly decreased bone mass density (femur: OR = −0.014, 95% CI = [−0.028, −0.001]; trochanter: OR = −0.016, 95% CI = [−0.028, −0.004]). The third tertile of 9-OH fluorene was associated with an increased likelihood of osteoporosis in women relative to the first tertile (overall: OR = 1.97, 95% CI = [1.07, 3.63]). Though the differences did not reach statistical significance, associations were strengthened in postmenopausal women relative to premenopausal women.	Associations between PAH exposure (including fluorene) and bone mass density or osteoporosis varied by bone site and menopausal status.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Chronic endocrine stress, inflammation, oxidative stress				
Verheyen et al. (2021) **(Belgium)** Cross-sectional study of 393 adolescents (183 males and 210 females with mean age = 14.8 yr) from the fourth Flemish Environment and Health Study (2016−2017).	Based on summed urinary levels of 2-OH fluorene and 3-OH fluorene.	Biomarkers of chronic endocrine stress (HCC), inflammation (NLR), and oxidative stress (8-oxodG in urine) were measured.	Combined fluorene metabolites were significantly positively associated with NLR (β = 1.06, 95% CI = [1.01, 1.13]). In sex-stratified analyses for NLR, associations in females were similar to the primary analysis, while associations in males were slightly attenuated (females: β = 1.10, 95% CI = [1.02, 1.18]; males: β = 1.02, 95% CI = [0.94, 1.10]).	Environmental exposure to PAHs (including fluorene) was associated with inflammation in adolescents.
Zhu et al. (2021) **(United States)** Longitudinal analysis of 19 healthy volunteers (11 males, 8 females, with overall mean age = 34 yr) over a 44-d study period.	Based on summed urinary levels of 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene.	Biomarkers of oxidative stress (diY, 8-OHdG, MDA, and four F2-isoprostane isomers [8-isoprostaglandinF2α, 11β-prostaglandinF2α, 15(R)-prostaglandinF2α, and 8-iso,15(R)-prostaglandinF2α]) were measured in urine.	Over the course of the study period, there were significant increases in levels of 8-OHdG (9.8%), MDA (12%), and diY (14%) attributed to every 1 unit increase in the log-transformed level of combined fluorene metabolites.	Continuous exposure to environmental PAHs (including fluorene) was associated with increased levels of oxidative stress.
Markers of Aged-Related Diseases				
Chen and Chen (2022) **(United States)** Cross-sectional study of 2,597 subjects (1,318 men and 1,279 women aged ≥20 yr) from NHANES (2015−2016).	Based on urinary levels of 2-OH fluorene and 3-OH fluorene.	Serum klotho levels were measured as a biomarker of premature aging.	In the total population, 3-OH fluorene was inversely associated with klotho (β = −0.026, 95% CI = [−0.046, −0.005]). In sex-stratified analyses, both metabolites were significantly associated with decreased serum klotho levels in men but not women (2-OH fluorene [men]: β = −0.014, 95% CI = [−0.027, 0.000]; [women]: β = −0.005, 95% CI = [−0.021, 0.011], 3-OH fluorene [men]: β = −0.034, 95% CI = [−0.059, −0.008]; [women]: β = −0.015, 95% CI = [−0.049, 0.018]).	Exposure to PAHs (including fluorene) was associated with decreased serum klotho levels.

Table 4. Selected Studies Evaluating Associations between Fluorene Exposure and Health Outcomes

Citation (Location); Study Type, Size and Description of Population	Methods for Fluorene Exposure	Methods for Outcome Assessment	Summary of Results[a]	Conclusions
Yang et al. (2023) **(United States)** Cross-sectional study of 1,460 subjects (716 men and 1,279 women aged ≥20 yr) from NHANES (2015−2016).	Based on urinary levels of 2-OH fluorene and 3-OH fluorene.	Telomere length of DNA obtained from blood samples was measured via quantitative polymerase chain reaction methods to calculate telomere length ratios relative to a standard reference.	Levels of 2-OH fluorene were significantly and inversely associated with telomere length (β = −0.01, 95% CI = [−0.1, −0.004]).	Exposure to PAHs (including fluorene) was associated with decreased telomere length.
Cancer				
Mwachiro et al. (2021) **(Kenya)** Cross-sectional analysis of 289 adults (158 males, 138 females; 157 aged <50 yr, 132 aged ≥50 yr) from the Study of Tenwek Esophageal Squamous Dysplasia Prevalence.	Based on levels of urinary 2-OH fluorene and 3-OH fluorene.	Esophageal squamous dysplasia was evaluated based on results from Lugol's iodine chromoendoscopy.	Positive, but nonsignificant, associations were detected between urinary fluorene metabolites and moderate or severe esophageal squamous dysplasia.	There were no significant associations between urinary fluorene metabolites and risk of moderate or severe esophageal squamous dysplasia.

[a]Significant results imply statistical significance at the level $p < 0.05$ as reported by the study authors. ORs and HRs are considered significant if the 95% CI does not include one; β (regression) coefficients and average interquartile differences of percent change ($\Delta_{\%}$) are considered significant if the 95% CI does not include zero. Differences in subpopulations are considered significant if the 95% CIs for the corresponding measurements do not overlap.

2-OH fluorene = 2-hydroxyfluorene; 3-OH fluorene = 3-hydroxyfluorene; 8-OHdG = 8-hydroxy-2'-deoxyguanosine; 8-oxodG = 8-oxo-7,8-dihydro-2'-deoxyguanosine; 9-OH fluorene = 9-hydroxyfluorene; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; diY = o,o′-dityrosine; DNA = deoxyribonucleic acid; FBS = fasting blood sugar; FEV_1 = forced expiratory volume of 1 second; FM% = fat mass percentage; FSH = follicle-stimulating hormone; FVC = forced vital capacity; GGT = gamma-glutamyl transpeptidase; GSH = glutathione; HCC = hair cortisol concentration; HDL-C = high-density lipoprotein cholesterol; HR = hazard ratio; LDH = lactate dehydrogenase; LDL-C = low-density lipoprotein cholesterol; LH = luteinizing hormone; MDA = malondialdehyde; MetS = metabolic syndrome; NHANES = National Health and Nutrition Examination Survey; NLR = neutrophil-lymphocyte ratio; OR = odds ratio; PAH = polycyclic aromatic hydrocarbon; PI = propidium iodide; PM2.5 = particulate matter 2.5; PS = phosphatidylserine; SD = standard deviation; TC = total cholesterol; TG = triglycerides; WBC = white blood cell.

2.2. ANIMAL STUDIES

2.2.1. Oral Exposures

The oral noncancer database for fluorene is limited to two subchronic gavage studies: (1) a 60-day study in male rats that evaluated behavioral endpoints (Peiffer et al., 2016) and (2) a 13-week study in male and female mice that evaluated a comprehensive set of toxicological endpoints (TRL, 1989), and two subchronic to chronic dietary studies: (1) 104- and 453-day studies in rats (sex unspecified) with limited data reported (Wilson et al., 1947) and (2) 6- and 18-month studies in female rats that evaluated a limited number of non-neoplastic endpoints (Morris et al., 1960). The TRL (1989) study was used by the IRIS program to derive a chronic oral reference dose (RfD) for fluorene (U.S. EPA, 1990).

Short-Term Studies

No studies were identified.

Subchronic Studies

Peiffer et al. (2016)

In a published, peer-reviewed study, Wistar rats (eight males/group, aged 8−9 weeks) were administered fluorene (98% pure) in vegetable oil (a mixture of sunflower, rapeseed, and grape seed oils with no PAH contamination) via gavage at 0 (vehicle control), 1, 10, or 100 mg/kg-day for 60 days. Body weights were recorded on Study Days 2, 7, 14, 21, and 28. Four behavioral tests, initiated on Study Day 28 and performed through Study Day 60, were conducted 30 minutes after daily gavage administration (during the dark phase of the circadian cycle). Tests included an elevated-plus maze test on Study Day 28 to evaluate anxiety, an open-field test on Study Day 29 to evaluate motor and exploratory activity, an eight-arm maze on Study Days 30−44 (7 days of food restriction, 3 days familiarization, and 5 days of testing) to evaluate spatial learning and memory, and an aversive light stimulus avoidance test (Test d'Evitement d'un Stimulus Lumieux Aversif, or TESLA) on Study Days 45−53 (7 days acclimatization, 1 day habituation, and 1 day of recall) to evaluate learning and memory. At sacrifice on Study Day 60, blood samples were collected, and brain and liver weights were recorded.

The outcomes measured in the elevated-plus maze (a raised maze consisting of three main areas: two open arms [ledges without enclosure] and two closed arms [ledges enclosed by vertical surrounding walls] intersecting at a central area to form a "plus" shape) included number of arm entries (total, open, and closed), time spent in each area (open arms, closed arms, and central area), total head dipping, percent head dipping in open arms, total rearing, and percent rearing in closed arms during a 5-minute period. Decreased open arm entries, decreased time spent in open arms, and increased occurrences of head dipping and rearing were considered indicative of anxiety.

In the open-field test, levels of activity on a platform containing 32 equivalent sections and three concentric zones (central, intermediate, and peripheral) were observed for 5 minutes and quantified by recording the numbers of squares crossed, number of rears, and amount of time spent in each zone.

The eight-arm maze, an enclosed maze consisting of eight arms (containing food pellets during the 5-day testing phase) joined in a central circular area, tested learning and spatial memory by measuring the ability of rats to position themselves within the maze using external

visual cues located within the testing room. Parameters evaluated included total time to complete the maze (time taken to visit each arm with a cutoff value at 15 minutes), total arm entries, arm entries before the first error, and number of arms visited per minute.

The TESLA evaluated reference memory. Rats were placed in a box with high-intensity lighting and two pedals: an active lever that turned off the light for a 30-second period and an inactive lever that did not turn the light off. The active lever is deactivated while the light is turned off and regains its active status after the light has been off for 30 seconds; cumulative lever presses of the deactivated active lever do not result in longer periods of light reduction. After 1 day of habituation, rats were observed for 20 minutes and reference memory was evaluated based on discrimination of the active lever, discrimination of the active (light) period, discrimination of the lever and the active period, and total number of lever presses.

Based on data presented for eight animals/group, it was presumed that no mortality occurred at any of the dosing levels (Peiffer et al., 2016). Body-weight data were not provided; however, percent body-weight gain (compared to the first day of treatment) was presented graphically with indicators of statistical significance. No statistically significant changes in body-weight gain measured on Study Days 2, 7, 14, 21, and 28 were observed for rats in the first two dose groups (1 and 10 mg/kg-day) relative to controls. Rats treated at the high dose of 100 mg/kg-day lost approximately 3 and 6% of their body weight by Study Days 2 and 7, respectively (based on analysis of the graphical data using the MATLAB tool, GRABIT[3]; see Table B-1), but then gained weight thereafter. Overall, rats in this group showed decreased percent weight gain relative to controls through Study Day 28 ($p < 0.01$ at each time point). The study authors reported that rats treated at the high dose exhibited lower average body weights throughout the 60-day study (data not shown). No treatment-related, toxicologically relevant effects on anxiety were observed based on the results of the elevated-plus maze; rats treated at the low dose (but not other doses) showed reduced anxiety (as evidenced by significantly decreased time spent in the closed arms and significantly increased time spent in the central area relative to controls) (Peiffer et al., 2016). Motor activity was unaffected by treatment (open-field test data not shown). In the eight-arm maze to evaluate learning and memory, a trend for decreased time to visit all arms ($p = 0.074$) as well as a statistically significant trend for the increase in the number of arms visited per minute ($p < 0.01$) were observed in all groups (including controls) based on the time of testing (i.e., all rats became more efficient at the maze as testing progressed). Rats treated at the high dose had fewer arm entries before the first error (i.e., performed worse in this behavioral test) compared to the other groups regardless of time of testing ($p = 0.098$). In addition to this overall effect, the only statistically significant interaction between time of testing and treatment group was for reduction in the number of arm entries before the first error ($p < 0.05$), which was particularly evident at the high dose (reduced by 24% on Study Day 5 relative to Study Day 1 compared to an 8% reduction in the control group and increases [i.e., improved performance] in the other dose groups). In the TESLA, another test that evaluated learning and memory, ability to discriminate between active (light) and inactive (dark) periods was significantly improved based on the time of testing for rats from all dosing groups (i.e., during testing relative to habituation; $p < 0.05$). The total number of lever presses increased based on treatment group (i.e., higher-dose groups typically had a higher number of lever

[3]GRABIT (https://www.mathworks.com/matlabcentral/fileexchange/7173-grabit) is an application of MATLAB and extracts data points from an image file using a graphical user interface.

presses; $p = 0.073$) and significantly decreased based on time of testing (i.e., there were fewer lever presses during testing than habituation; $p < 0.01$). There were no statistically significant interactions between treatment group and time of testing for this effect or any of the other TESLA endpoints. Based on overall results from the behavioral battery, the study authors concluded that learning and memory were not affected by treatment.

Absolute brain and liver weights were not reported (Peiffer et al., 2016). Relative brain and liver weight data were presented graphically by dose group, with indicators of statistical significance for treatment groups relative to the control group. Nonsignificant increases in relative brain weight were observed at the mid and high dose (4 and 8% higher than controls, respectively). Relative liver weight showed statistically significant increases ($p < 0.05$) at all doses (by approximately 6, 17, and 37% relative to controls at 1, 10, and 100 mg/kg-day, respectively, based on analyses using the MATLAB tool, GRABIT; see Table B-1). Increases in relative liver weight at the mid and high doses (10 and 100 mg/kg-day) were considered to be biologically significant.

Limitations of the study include the lack of data reported for biological endpoints of interest, including absolute brain and liver weights at study termination. Data were presented graphically, but not reported numerically, for relative brain and liver weights as well as body weights measured on Study Days 2, 7, 14, 21, and 28. No clinical chemistry evaluations or histological examinations were performed. Despite these limitations, a NOAEL of 1 mg/kg-day is identified from these data based on biologically significant (>10%) increases in relative liver weight in male rats at 10 and 100 mg/kg-day, which were also reported to be statistically significant ($p < 0.01$). The administered doses of 0, 1, 10, and 100 mg/kg-day correspond to human equivalent doses (HEDs) of 0, 0.2, 2.4, and 23.6 mg/kg-day, respectively[4].

TRL (1989) [cited as U.S. EPA, 1989 by U.S. EPA (1990)]

In an unpublished, non-peer reviewed study, Crl:CD-1 mice (20/sex/group, aged 35 days) were administered fluorene (>98% pure) in corn oil via daily gavage at 0 (vehicle control), 125, 250, or 500 mg/kg-day for 13 weeks. Additional groups of five animals/sex were designated as satellite animals; these animals were dosed in parallel to the main group and, if necessary, used as substitutes for animals lost by technical error. Endpoints evaluated included mortality, clinical signs of toxicity, ophthalmologic examinations, food consumption, body weight, hematology (red blood cell [RBC] count, total and differential white blood cell [WBC] count, reticulocyte counts if animals exhibited signs of anemia, hemoglobin, RBC packed cell volume [PCV], mean cell volume [MCV], mean cell hemoglobin [MCH], and mean cell hemoglobin concentration [MCHC]) and clinical chemistry (glucose, blood urea nitrogen [BUN], cholesterol, total bilirubin, total protein, albumin, globulin, albumin/globulin ratio, sodium, potassium, chloride, total carbon dioxide, and the activities of alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], and lactate dehydrogenase [LDH]) in 10 mice/sex/group. Organ weights (brain, heart, liver, spleen, kidneys, and testes; as paired organs when applicable) and gross and microscopic pathology (~40 tissues in control animals, high-dose animals, and animals that died or were sacrificed moribund; liver, lungs, spleen,

[4]Administered doses were converted to HEDs by multiplying by a dosimetric adjustment factor (DAF) of 0.236 calculated as follows: DAF = $(BW_a^{1/4} \div BW_h^{1/4})$, where BW_a = animal body weight, and BW_h = human body weight. In the absence of data for study-specific time-weighted average (TWA) animal body weights, the reference value for the body weight of male Wistar rats in a subchronic study of 0.217 kg was used (U.S. EPA, 1988). For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).

kidneys, testes, and gross lesions of low- and mid-dose animals) were also evaluated. Only one member of an organ pair (with the exception of the thyroid gland) was examined unless a potentially treatment-related lesion was detected.

Six animals died during the study (TRL, 1989). Two high-dose females that died during Week 1 were replaced with animals from the satellite group; the others (one control male during Week 3 and one control, one low-dose, and one-high dose female during Weeks 5, 7, and 9, respectively) were not replaced; upon histological examination, all deaths were attributed to gavage error. Overall survival was not significantly different among groups, including controls. Clinical signs of toxicity with significantly increased incidence compared to controls in both males and females included salivation (all treated groups) and hypoactivity (high-dose group only) (see Table B-2). Other clinical signs noted (but not significantly increased) were labored respiration in high-dose animals of both sexes and ptosis, urine wet abdomen, and unkempt appearance, predominantly in high-dose males but also seen in other dose groups. The study authors indicated that retinal degeneration observed at Week 13 was spontaneous rather than treatment-related; however, data (including the numbers of animals and dose groups affected) were not shown. Significantly increased food consumption was observed in mid- and high-dose males (8−22% higher than controls) and high-dose females (8−19% higher than controls) for most weeks of the study (see Table B-3). Significantly increased food consumption was also observed (albeit less frequently) in low-dose males and mid-dose females. No significant effects on body weight occurred in males (see Table B-4). In females, small, statistically significant increases in body weight were observed at the high dose (6−8% higher than controls) for most weeks of the study (especially starting on Week 5). There were no statistically significant effects on body weight in females treated at the low or mid dose. During the duration of the study (Weeks 1−13), high-dose males and females gained 20 and 30% more weight than controls, respectively (see Table B-4).

Hematological changes indicative of anemia included significant reductions in RBC count (10−21% lower than controls in high-dose males and mid- and high-dose females), PCV (10−22% lower than controls in mid- and high-dose males and females), and hemoglobin (16 and 13% lower than controls in high-dose males and females, respectively) (see Table B-5) (TRL, 1989). There were small (<10%), but statistically significant, increases in some of the calculated RBC indices (MCV, MCH, and MCHC), primarily in the mid- and/or high-dose groups. WBC count was significantly increased in high-dose females (46% higher than controls) but was within the range of natural variation as measured within the study; differential WBC counts (i.e., neutrophil, monocyte, eosinophil, and basophil counts) were not significantly impacted by treatment. Significant clinical chemistry effects observed in mid- and/or high-dose males and females included increased serum cholesterol (≥25% higher than controls), decreased BUN (20−24% lower than controls), and increased total bilirubin (61−71% higher than controls); statistically significant trends for decreased BUN and increased bilirubin were also reported (see Table B-6). Other statistically significant changes in clinical chemistry parameters (i.e., potassium levels and the activities of ALT and ALP) were not considered treatment-related for one or more of the following reasons: the magnitude of change was small (within range of natural variation), changes were not dose-related, changes were not consistent across sexes or endpoints (e.g., changes in serum ALT were not accompanied by changes in other parameters indicative of liver cell damage, such as serum AST or LDH), and/or changes were of uncertain toxicological significance.

Significant effects on organ weights are shown in Table B-7 (TRL, 1989). In males, absolute and relative liver weights were biologically and statistically significantly increased at the mid and high dose (by 17−35% relative to controls). Relative (but not absolute) liver weight was statistically significantly increased at the low dose; however, the magnitude of change was small (7% higher than controls). Significant increases in absolute and relative kidney weight were observed in high-dose males only (12 and 8% higher than controls, respectively). Large and statistically significant increases in absolute and relative spleen weights were observed at the mid dose (28−31% higher than controls) and at the high dose (99−106% higher than controls). In females, absolute and relative liver weights were biologically and statistically significantly increased at the mid dose (21−25% higher than controls) and the high dose (35−45% higher than controls); relative liver weight was slightly, but statistically significantly, increased at the low dose (8% higher than controls). No treatment-related effects on kidney weights were observed. Absolute and relative spleen weights were increased by 33−35% relative to controls in mid-dose females and by 84−99% relative to controls in high-dose females. There were no significant changes in absolute brain weight; however, a slight, but significant, decrease in relative brain weight (9% lower than controls) was observed in high-dose females. This effect was attributed by the study authors to increased body weight of high-dose females at necropsy (8% higher than controls).

No treatment-related effects were observed at gross necropsy (TRL, 1989). Microscopic examination revealed significant increases in histopathological effects in male mice, including increased incidences of brown pigment (with an appearance reminiscent of hemosiderin) in Kupffer cells, centrilobular cytomegaly (i.e., enlarged hepatocytes), and centrilobular cytological alterations (more homogeneous and eosinophilic cytoplasm) in the livers of high-dose males; significant increases in the incidence and severity of hemosiderosis and hematopoietic cell proliferation in the spleens of mid- and high-dose males; and degenerative lesions (characterized by the presence of giant spermatid cells) in the testes of high-dose males (see Table B-8). The latter effect was accompanied by observations of hypospermia in 2/20 high-dose males (compared to 0/20 controls). In females, a nonsignificant increased incidence of liver pigmentation was observed in high-dose females (4/20 at the high dose compared to 0/20 for controls). The incidence and severity of hemosiderosis of the spleen were significantly increased in all groups of treated females; the incidence and severity of hematopoietic cell proliferation were significantly increased in mid- and high-dose females only.

The changes in hematology and clinical chemistry parameters were consistent with the organ weight changes and histopathological effects seen in the liver and spleen. Effects in the mid- and/or high-dose males and females included decreased RBC count, PCV, and hemoglobin; increased serum total bilirubin and cholesterol and decreased BUN; increased absolute and relative liver and spleen weights; and histopathological changes in the liver (pigmentation in Kupffer cells, centrilobular cytomegaly, and cytoplasmic alterations) and spleen (hemosiderosis and hematopoietic cell proliferation). Although an increased incidence of minimal hemosiderosis was also observed in low-dose females, it was not considered to be biologically relevant due to the absence of hematological changes and hematopoietic cell proliferation suggestive of RBC destruction and restorative proliferation. The NOAEL and LOAEL values based on biologically relevant effects are 125 and 250 mg/kg-day, respectively. The administered doses of 0, 125, 250,

and 500 mg/kg-day correspond to HEDs of 0, 18.3, 36.6, and 73.7 mg/kg-day for males, and 0, 17.4, 34.7, and 70.1 mg/kg-day for females[5].

Wilson et al. (1947)

Groups of rats (sex, strain, and number not specified) were administered fluorene (purity not specified) in the diet for 104 days. Exposure concentrations ranged from 65.74 to 1,060 mg/kg-day (equivalent to approximately 0.062−1.0% [unspecified number of dosage levels]) in the diet[6]. There was no indication that a control group was used and the comparison group for effects reporting in fluorene-treated rats was not specified. Effects reported in fluorene-treated rats (and the concentrations at which they were observed, when specified) included yellow staining of the fur near the urethra, significantly decreased growth (at 530 and 1,060 mg/kg-day), increased liver weight (≥265.1 mg/kg-day), decreased spleen weights (all concentrations), and decreased testes weight (at 1,060 mg/kg-day). It was indicated that animals appeared normal, and that there were no significant changes in gross or microscopic pathology. The lack of detailed reporting precludes the identification of effect levels for this study; accordingly, it is not summarized in Table 3.

Chronic Studies

Wilson et al. (1947)

Wilson et al. (1947) reported a second experiment in which groups of rats (sex, strain, and number not specified) were administered fluorene (purity not specified) at 0.125, 0.25, or 0.5% in the diet for 453 days. These concentrations are equivalent to approximately 104.7, 209.5, and 419 mg/kg-day, respectively[7]. There was no indication that a control group was used. No treatment-related effects on body weight or gross pathology were observed (data not shown). Fluorene-treated rats showed yellow staining of the fur and histological effects in the lung (inflammation and/or metaplasia of the bronchial epithelium; not considered by the study authors to be treatment-related), heart (pericarditis), urinary bladder (worms), and testes (moderate atrophy). A small benign tubular adenoma of the kidney was also noted in one of the low-dose animals. The lack of detailed reporting precludes the identification of effect levels for this study; accordingly, it is not summarized in Table 3.

Morris et al. (1960)

Groups of Buffalo strain rats (18−20 females/group) were administered fluorene (stated to be "highly purified") at 0.05% in the diet for 6 months (diet low in protein and fat and containing 3% propylene glycol) or 18 months (diet containing natural foodstuffs and 3% corn oil) (Morris et al., 1960). The study authors reported that the daily average intakes and the total intakes of fluorene per rat were 4.3 and 796 mg, respectively, for the 6-month study and 4.6 and

[5]Administered doses were converted to HEDs by multiplying by DAFs of 0.146, 0.146, and 0.147 for low-, mid-, and high-dose males and 0.139, 0.139, and 0.140 for low-, mid-, and high-dose females calculated as follows: $DAF = (BW_a^{1/4} \div BW_h^{1/4})$, where BW_a = animal body weight, and BW_h = human body weight. Study-specific TWA animal body weights of 0.032, 0.032, and 0.033 kg for low-, mid-, and high-dose males, respectively, and 0.026, 0.026, and 0.027 kg for low-, mid-, and high-dose females, respectively, were used (U.S. EPA, 1988). For humans, the reference value of 70 kg was used for body weight, as recommended by U.S. EPA (1988).

[6]Dose estimates were calculated using reference values for food consumption and body weight (U.S. EPA, 1988). The reference body weight and food consumption values for male and female rats (unspecified strain, averaged across sexes) in a subchronic study are 0.152 kg and 0.0161 kg/day, respectively.

[7]Dose estimates were calculated using reference values for food consumption and body weight (U.S. EPA, 1988). The reference body weight and food consumption values for male and female rats (unspecified strain, averaged across sexes) in a chronic study are 0.305 kg and 0.0255 kg/day, respectively.

2,553 mg, respectively, for the 18-month study. These daily intakes are equivalent to approximately 18.8 mg/kg-day for the 6-month study and 20.1 mg/kg-day for the 18-month study[8]. Two groups of control animals were fed diets containing 3% propylene glycol or 3% corn oil for about 12 months. The age of animals at study initiation was variable (0.9 and 3.0 months in the fluorene-treated groups; 1.8 and 3.5 months in the control groups). Animals were monitored daily for mortality and clinical signs of toxicity. Body weights and food consumption were measured weekly. At study termination, all animals were subjected to necropsy; tissues (number not specified) were examined microscopically in 11/20 animals from the 6-month study and 18/18 animals from the 18-month study (as the tissues of these animals were deemed "satisfactory for microscopic examinations").

No data for mortality, clinical signs of toxicity, body weights, food consumption, or gross pathology were reported (Morris et al., 1960). Non-neoplastic lesions in rats treated with fluorene for 6 months included acanthosis and hyperkeratosis of the forestomach (incidence: 5/11), squamous metaplasia of the kidney (incidence: 7/11) and uterus (incidence: 1/11), epithelial ulcer of the small intestine (incidence: 1/11), and cirrhosis of the liver (incidence: 3/11). Neoplastic lesions in rats treated for 6 months were squamous cell carcinomas of the kidney (incidence: 1/11) and ureter (incidence: 1/11). Non-neoplastic lesions in rats treated for 18 months were limited to hyperplasia of the pituitary (incidence: 2/18). Neoplastic lesions in rats treated for 18 months were fibrosarcoma of the uterus (incidence: 1/18), carcinosarcoma of the uterus (incidence: 1/18), granulocytic leukemia of the reticuloendothelial system (incidence: 1/18), and adenoma of the pituitary (incidence: 4/18). None of these lesions were reported in controls. Lesions seen in the 6-month study were not observed in the 18-month study; it is possible that these effects might be attributed to the composition of the diet and/or the vehicle used (propylene glycol or corn oil). Limitations associated with the study (including incomplete data reporting, lack of concurrent control groups, and confounding factors such as the vehicle/diet and the age of the animals at study initiation) precludes the identification of effect levels for this study; accordingly, it is not summarized in Table 3.

Reproductive and Developmental Studies

No studies were identified.

2.2.2. Inhalation Exposures

The noncancer inhalation toxicity database of fluorene is limited to a short-term study that evaluated effects on behavior in fluorene-exposed rats (Peiffer et al., 2013).

Short-Term Studies

Peiffer et al. (2013)

In a published, peer-reviewed study that adhered to OECD guidelines (OECD Test Guideline [TG] 403), male Wistar Han rats (18/group, aged 8−9 weeks) were exposed nose-only to fluorene (purity ≥99%) as a vapor at target concentrations of 0 (air control), 1.5, or 150 ppb (0, 0.010, or 1.02 mg/m^3)[9] 6 hours/day, 7 days/week, for 2 weeks. To discriminate between stress- and treatment-related effects, two control groups were employed. One group of controls was exposed via inhalation tubes (restrained controls); the other was exposed in chambers that

[8]Dose estimates were calculated using a reference value for body weight (U.S. EPA, 1988). The reference body weight value for female rats (unspecified strain) in a chronic study is 0.229 kg.

[9]Values in the study report were given in ppb. Values in mg/m^3 = exposure in ppm × molecular weight (MW) of fluorene ÷ 24.45. The MW of fluorene is 166.22 g/mol (U.S. EPA, 2021b).

permitted movement (freely moving rats). Rats designated to the restrained control and fluorene-exposed groups were habituated to exposure conditions for 8 days prior to initiation of the study. Parameters measured to evaluate the stress response in control rats included body weights, blood corticosterone levels (at four time points: prior to habituation, on the day prior to initiation of exposure, after 7 days of exposure, and after 14 days of exposure), and brain, liver, and adrenal gland weights (after 14 days of exposure). During each exposure period, fluorene concentrations, temperature, and relative humidity were monitored. Following the last exposure, 12 rats/group were used for neurobehavioral analyses (conducted during the dark phase of the circadian cycle); the remaining 6 rats/group were used for measurements of blood and brain levels of fluorene and mono-hydroxylated metabolites. In addition to the open-field test to evaluate locomotor activity, the elevated-plus maze to evaluate anxiety, and the eight-arm maze to evaluate learning and spatial memory (3 days of acclimatization and 12 days of testing), performed as described by (Peiffer et al., 2016) in Section 2.2.1, short-term memory was evaluated in the Y-maze. The parameters measured in the Y-maze (a maze formed by three arms) included the percent spontaneous alternation (as a measurement of working memory) and numbers of total arm entries, arms visited per minute, and arm entries in the first minute (as measurements of activity).

Based on data presented for 6 or 12 animals/group, it was presumed that no mortality occurred at any of the dosing levels (Peiffer et al., 2013). No fluorene was detectable in the control chambers (both control groups). Measured fluorene concentrations were 1.30−1.60 ppb (0.00884−0.0109 mg/m^3) in the low exposure group and 144.3−157.2 ppb (0.9810−1.069 mg/m^3) in the high-exposure group. Measured fluorene concentrations in the low-exposure group did not vary significantly from the target concentration; however, measured fluorene concentrations at the high concentration were slightly higher than the target concentration on Day 1 and slightly lower than the target concentration on Day 4 (see Table B-9). During exposure, temperature and relative humidity measurements did not differ significantly from target values (22 ± 1°C and 55 ± 10%, respectively).

Most physiological parameters used to evaluate restraint stress did not vary significantly among freely moving rats and restrained controls (i.e., blood corticosterone levels and relative brain, liver, and adrenal gland weights) (Peiffer et al., 2013). The body weights of restrained controls were slightly, but statistically significantly, decreased at three of the four measured time points (4−6% lower than freely moving controls) (see Table B-10). Data for body and organ weights in fluorene-exposed rats were not reported. Anxiety and memory-related behaviors were reportedly unaffected by restraint stress (presumably based on results from the elevated-plus and eight-arm mazes; data not shown). Restrained controls showed a significant increase in the total number of crossed squares in the open-field test (27% higher than freely moving controls) and the total arms visited in the Y-maze (29% higher than freely moving controls). The study authors reported that these results indicated that restrained controls displayed a nonspecific increase in activity compared to freely moving controls in the absence of detrimental effects on physiological parameters, anxiety, or learning.

The results of neurobehavioral tests in fluorene-exposed rats compared to freely moving controls were not provided (Peiffer et al., 2013). Compared to restrained controls, rats exposed to fluorene (both exposure groups) showed significantly increased numbers of crossed squares in the central (unprotected) area of the open-field test (78−87% higher than controls); rats exposed at the low concentration also spent significantly more time in the central area (69% higher than controls) (based on analyses using the MATLAB tool, GRABIT; see Table B-11). The study

authors reported that these results were indicative of decreased anxiety in fluorene-exposed rats. However, these effects were not dose-related, and there were no statistically significant effects on other open-field test parameters (including the total number of crossed squares). In the elevated-plus maze, another test that evaluated anxiety, rats exposed to fluorene spent significantly more time in the central (decision-making) area compared to restrained controls (20−25% higher than controls); a decreased percentage of head dipping in the open area was also reported (p = 0.08). These effects occurred in the absence of significant differences in open and closed arm times, total head dipping, or other parameters (i.e., providing no evidence of decreased anxiety in fluorene-exposed rats). In the eight-arm maze (data not shown), reductions in the total time required to visit all arms and total numbers of arm entries and significant increases in arm entries before first error and numbers of arms visited per minute during the exposure period (i.e., based on time of testing from Day 1 to 12) were observed in both restrained controls and fluorene-exposed rats; there were no significant differences among exposed rats and controls. Results from the Y-maze test showed that the percentage of spontaneous alteration was not significantly impacted by exposure; activity parameters were likewise unaffected. Although standard toxicological endpoints (e.g., body weights, clinical chemistry parameters, organ weights, and gross or microscopic pathology) were not measured in fluorene-exposed rats, behavioral endpoints were evaluated. A free-standing NOAEL of 1 mg/m^3 (the highest tested concentration) was identified based on no effects on behavioral endpoints in male rats. The concentrations of 0, 0.010, and 1.02 mg/m^3 correspond to human equivalent concentrations (HECs) of 0, 0.003, and 0.3 mg/m^3, respectively[10].

Subchronic Studies

No studies were identified.

Chronic Studies

No studies were identified.

Reproductive and Developmental Studies

No studies were identified.

2.3. OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tables 5A and 5B provide overviews of other supporting studies of fluorene and metabolism/toxicokinetic studies of fluorene, respectively.

[10]The HEC was calculated using the equation for extrarespiratory effects from a Category 3 Gas (U.S. EPA, 1994): HEC_{ER} = continuous concentration in mg/m^3 × ratio of animal:human blood gas partition coefficients. A default value of 1 applied was applied due to the lack of data for partition coefficients for fluorene in humans and rats.

Table 5A. Other Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Supporting animal studies				
Acute i.p. exposure	Not reported.	Mouse LD_{50} >2,000 mg/kg (no further details were available).	The acute toxicity of fluorene is low via the i.p. route of exposure.	NLM (2021)
Subchronic i.p. exposure	Male Wistar rats (eight/group) were exposed to fluorene via gavage at 0, 1, 10, or 100 mg/kg-d for 60 d. Body weights were measured regularly (reported through Study Day 28). On Study Days 28−60, rats were subjected to behavioral tests (open field test to evaluate motor activity, elevated-plus maze to evaluate anxiety, and an eight-arm maze and TESLA to evaluate learning and memory). Brain and liver weights were recorded.	Rats treated at the high dose lost weight during the first week of treatment and showed decreased body-weight gain (approximately 5%) relative to controls through Day 28. Rats treated at the low and mid dose showed decreased anxiety (based on significantly more time spent in the central unprotected area of the elevated-plus maze). Locomotor activity and learning ability were unaffected by treatment. Relative liver weight was biologically and statistically significantly increased (by approximately 30% as estimated from graphical data; $p < 0.01$) at the high dose only. Relative brain weight was not significantly impacted by treatment.	Low doses of fluorene decreased anxiety, with no effect on motor activity or learning; the highest dose of fluorene caused decreased body weight gain and increased relative liver weight.	Peiffer et al. (2016)
Mode of action/mechanistic				
In ovo	White leghorn chicken eggs ($n \geq 10$/group) were exposed to fluorene (total dose: 1.36 mg/egg or 300 mg/kg) via three daily injections into the air sac on Days 9−11 of incubation. Viability, fetal weights, liver weights, and liver histopathology were evaluated at study termination (Day 12 or 18).	Viability was 93% in the fluorene-treated group. No significant effects on fetal weights, absolute or relative fetal liver weights, or liver histology were observed on Days 12 or 18 relative to control groups.	No developmental anomalies were observed in chickens treated in ovo with fluorene.	Iatropoulos et al. (2017)

Table 5A. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Cytotoxicity	HepG2 cells were exposed to fluorene at 0, 25, or 50 µg/mL for 3 d with or without metabolic activation. Cytotoxicity was measured via neutral red assay.	Cytotoxicity was 115 and 108% of controls at 25 and 50 µg/mL, respectively, in the absence of activation and 105 and 101% of controls at 25 and 50 µg/mL, respectively, in the presence of activation.	Fluorene was not cytotoxic in a human liver tumor cell line.	Babich et al. (1988)
Cytotoxicity	Rat hepatocytes were exposed to fluorene at 10^{-4} M. Cell damage was measured as a function of LDH levels.	LDH activity was increased by about 20% relative to controls; variation of up to 15% was observed in duplicate cultures.	Fluorene induced little cytotoxicity in rat hepatocytes.	Mcqueen and Williams (1982)
CYP induction	CYP1A1 induction (as measured by EROD) was evaluated in rat hepatocytes.	No CYP1A1-catalzyed EROD activity was observed in fluorene-treated hepatocytes.	Fluorene was not an inducer of CYP1A1 in rat hepatocytes.	Till et al. (1999)

CYP = cytochrome; EROD = 7-ethoxyresorufin-*O*-deethylase; i.p. = intraperitoneal; LD_{50} = median lethal dose; LDH = lactate dehydrogenase; TESLA = Test d'Evitement d'un Stimulus Aversif (avoidance test of an adverse light stimulus).

Table 5B. Metabolism and Toxicokinetic Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Human studies				
Human (dietary)	The excretion half-times of mono-hydroxylated metabolites were determined in nine nonsmoking volunteers, aged 23−61 yr (no occupational exposure to PAHs), administered a PAH-containing lunch. Urine samples were collected 15 h before exposure to 60 h after exposure.	Urinary 9-OH fluorene, 3-OH fluorene, and 2-OH fluorene were increased by a median of 27-, 36-, and 28-fold, respectively, from pre-exposure to post-exposure. The observed time to reach maximum urinary fluorene metabolite concentrations (t_{max}) was 3.8−3.9 h after exposure. Modeled median elimination half-time values were 3.1, 6.1, and 2.9 h for 9-OH fluorene, 3-OH fluorene, and 2-OH fluorene, respectively.	Urinary levels of OH metabolites increased rapidly after exposure and returned to background levels 24−48 h after exposure.	Li et al. (2012)
Human (dietary, inhalation, dermal)	Twenty male subjects were exposed to PAHs via outdoor barbeque for 2.5 h. Dietary, inhalation, and dermal exposures occurred via ingestion of grilled food, intake of atmospheric PAHs, and absorption of PAH fumes from exposed skin and clothing, respectively. Subjects were divided into three groups: Group A = dietary, dermal, and inhalation exposure (cooked and ate barbeque; *n* = 7), Group B = dermal and inhalation exposure (cooked but did not eat barbeque; *n* = 7), and Group C = dermal absorption only (cooked barbeque while wearing protective hood; *n* = 6). Food, clothing, and air samples were collected and analyzed for PAH. Urine samples, collected prior to exposure and for 35 h following exposure, were evaluated for hydroxylated metabolites (including 2-OH fluorene).	Peak levels of OH metabolites in the urine were seen within 10 h of exposure, declining to initial levels within 24 h. Urinary levels of OH metabolites were increased the most by dietary exposure (Group A−Group B), but also increased by dermal and/or inhalation exposure (Groups B and C). Ratios of excretion to intake via the dietary, dermal, dermal + inhalation, and inhalation routes were 0.38, 0.11, 0.11, and 0.097, respectively. Dermal absorption was estimated by the study authors to account for a higher proportion of dermal + inhalation intake than inhalation (61%, compared to 39% via inhalation).	Urinary levels of PAH metabolites (including 2-OH fluorene) increased rapidly in the urine and returned to initial levels within 24 h after exposure. Ratios of excretion to intake provided evidence for the highest availability of PAHs (including fluorene) from dietary exposure; availability was higher via dermal absorption than inhalation exposure for low molecular weight PAHs (including fluorene).	Lao et al. (2018)

Table 5B. Metabolism and Toxicokinetic Studies

Test	Materials and Methods	Results	Conclusions	References
Human (inhalation and/or dermal)	Firefighters (37 males and 4 females) responding to controlled residential fires were monitored for urinary levels of PAH metabolites (including hydroxylated fluorenes) at pre- and post-firefighting time points.	Median urinary concentrations of summed hydroxylated fluorenes increased significantly at the post-firefighting time point (relative to the pre-firefighting time point); peak excretion occurred 3 h after exposure.	Urinary PAH metabolite concentrations (including fluorene metabolites) increased rapidly after exposure. Dermal absorption likely contributed to fluorene exposure, as workers protected their airways using SCBA.	Fent et al. (2019)
Human (inhalation and/or dermal)	Levels of mono-hydroxylated metabolites of fluorene (2-OH fluorene, 3-OH fluorene, and 9-OH fluorene) were measured in the urine of six firefighting instructors who completed five 2-h training sessions.	Concentrations of summed fluorene metabolites in the urine increased after training sessions, peaking at approximately 1 h (9-OH fluorene) or 3 h (2-OH fluorene and 3-OH fluorene) after the end of training. Estimated elimination half-lives for 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene were 4.8, 9.3, and 3.5 h, respectively.	Fire training is associated with rapid uptake of PAHs, including fluorene. Based on SCBA use, dermal absorption is presumed to be a significant route of exposure.	Rossbach et al. (2020)
Human (unspecified)	Human tissue samples (brain, liver kidney, lung, heart, spleen, and abdominal fat), obtained from eight cadavers at autopsy, were evaluated for levels of PAHs, including fluorene.	Fluorene was detected in 88% of liver, lung, and abdominal fat samples and 100% of brain, kidney, heart, and spleen samples. Concentrations of fluorene were highest in abdominal fat > heart > brain > kidney > liver > lung > spleen.	PAHs, including fluorene, are distributed throughout the body and accumulate preferentially in fatty tissues.	Pastor-Belda et al. (2019)
Human (unspecified)	Urinary levels of mono-hydroxylated PAH metabolites (including 2-OH fluorene) were measured in 218 children (aged 3 yr) in Krakow, Poland.	2-OH fluorene was present in nearly all samples. Higher 2-OH fluorene concentrations were associated with exposure to environmental tobacco smoke and gas-based appliances.	Monitoring urinary 2-OH fluorene can be used to evaluate fluorene exposure.	Sochacka-Tatara et al. (2018)

Table 5B. Metabolism and Toxicokinetic Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
Animal studies				
Short-term inhalation exposure	Male Wistar Han rats (18/group) exposed to fluorene nose-only as a vapor at 0, 1.5, or 150 ppb (0, 0.010, or 1.02 mg/m^3) 6 h/d, 7 d/wk for 2 wk. At the end of the 2-wk exposure period, blood and brain levels of fluorene, 9-OH fluorene, 3-OH fluorene, and 2-OH fluorene were measured in six rats/group.	Blood (plasma): • Mean levels of fluorene were similar to controls (background) in all treated groups. • 2-OH fluorene was significantly increased at both exposure concentrations. • 9-OH fluorene and 3-OH fluorene were significantly increased at the high concentration. Brain: • Mean fluorene levels were significantly decreased at both exposure concentrations. • 9-OH fluorene and 2-OH fluorene were significantly increased at the high concentration. • 3-OH fluorene was not detected (in exposed rats or controls).	Hydroxylated metabolites of fluorene were detected in a dose-related manner in the blood and brain of rats following inhalation exposure.	Peiffer et al. (2013)
Subchronic oral (gavage) or i.p. exposure	Male Wistar rats (eight per group) were exposed to fluorene via gavage or i.p. injection at 0, 1, 10, or 100 mg/kg-d for 60 d. At the end of the 60-d exposure period, plasma and brain tissue were evaluated for levels of fluorene, 9-OH fluorene, 2-OH fluorene, and 3-OH fluorene.	Gavage– Blood (plasma): • Plasma fluorene levels were similar to controls (background) in all treated groups. • Levels of all three metabolites were significantly increased in all treatment groups in a dose-related manner. Brain: • Fluorene and 2-OH fluorene were significantly increased in all treated groups (and 9-OH fluorene in the mid- and high-dose groups) in a dose-related manner. • Levels of 3-OH fluorene were below the limit of detection in all groups (including controls).	Fluorene and/or its hydroxylated metabolites were detected in a dose-related manner in the blood and/or brain of rats following i.p. or gavage exposure.	Peiffer et al. (2016)

Table 5B. Metabolism and Toxicokinetic Studies				
Test	**Materials and Methods**	**Results**	**Conclusions**	**References**
		Injection− Blood (plasma): • Plasma fluorene levels were significantly increased at the high dose. • 2-OH fluorene and 3-OH fluorene were significantly increased at all doses (and 9-OH fluorene was significantly increased at the mid and high dose) in a dose-related manner. Brain: • Fluorene levels were significantly increased at the mid and high dose (dose-related). • 2-OH fluorene and 9-OH fluorene levels were significantly increased at all doses (dose-related). • 3-OH fluorene was not detected (in treated rats or controls).		
In vitro				
Rat liver microsomes	Rat liver preparations (S9) were incubated with fluorene at 37°C for 20 min; metabolites were identified by UV spectra, mass spectrometry, and comparison to reference standards.	Metabolites of fluorene included 9-fluorenol (9-OH fluorene), 1-OH fluorene, and 9-fluorenone. Fluorene also reacts with oxygen to form a hydroperoxide.	Metabolites of fluorene include 1-OH fluorene, 9-OH fluorene, 9-fluorenone, and hydroperoxides. It is unknown if these hydroperoxides are a direct or indirect product of metabolism.	IARC (1983); LaVoie et al. (1981)

1-OH fluorene = 1-hydroxyfluorene; 2-OH fluorene = 2-hydroxyfluorene; 3-OH fluorene = 3-hydroxyfluorene; 9-OH fluorene = 9-hydroxyfluorene; i.p. = intraperitoneal; PAH = polycyclic aromatic hydrocarbon; SCBA = self-contained breathing apparatus; UV = ultraviolet.

2.3.1. Supporting Animal Studies

The database of supporting animal studies for fluorene comprises two intraperitoneal (i.p.) exposures: one acute (NLM, 2021) and one subchronic (Peiffer et al., 2016) (see Table 5A). The acute toxicity of fluorene is low via the i.p. route of exposure (based on a mouse median lethal dose [LD_{50}] >2,000 mg/kg) (NLM, 2021). No further information on this study or other acute toxicity studies was located.

A subchronic toxicity study conducted via the i.p. route of exposure showed effects consistent with those observed in the subchronic gavage toxicity study that was run in parallel (Peiffer et al., 2016). As in the gavage study, male rats treated via i.p. injection showed evidence of decreased anxiety at low doses (at 1 mg/kg-day and at 1 and 10 mg/kg-day, respectively) without significant effects on learning or memory. However, there were significant toxicologically relevant systemic effects at the highest dose only (100 mg/kg-day); relative to the controls, statistically significant reduced weight gain was observed across time points and relative liver weight was reported to be significantly increased, both statistically and biologically (14% increase).

2.3.2. Mode-of-Action/Mechanistic Studies

Table 5A provides an overview of mode of action/mechanistic studies. Few noncancer mechanistic studies were identified. In studies conducted in human HepG2 cells and rat hepatocytes, fluorene exhibited little to no cytotoxicity (Babich et al., 1988; Mcqueen and Williams, 1982); fluorene also did not significantly induce CYP1A1 in rat hepatocytes (Till et al., 1999). Treatment of chicken eggs with fluorene in ovo had no significant effect on viability and did not induce developmental anomalies (i.e., no effects on fetal weight, absolute or relative fetal liver weights, or liver pathology were observed) (Iatropoulos et al., 2017).

2.3.3. Metabolism/Toxicokinetic Studies

Table 5B provides an overview of metabolism/toxicokinetic studies of fluorene. PAHs are absorbed via oral, inhalation, and dermal exposure. Absorption is influenced by the vehicle of administration and/or the lipophilicity of the compound (ATSDR, 1995). Data for fluorene (log K_{ow} of 4.18) suggest that it is absorbed rapidly via all routes. Fluorene metabolites have been detected in the tissues and urine of humans exposed to PAHs via the oral, inhalation, and/or dermal routes of exposure, with urinary levels peaking within 1−10 hours of exposure, providing evidence of rapid absorption (Rossbach et al., 2020; Fent et al., 2019; Pastor-Belda et al., 2019; Lao et al., 2018; Sochacka-Tatara et al., 2018; Li et al., 2012). In most tissues, but especially in urine, hydroxylated metabolites are present as glucuronide and sulfate conjugates. Based on ratios of excretion of fluorene metabolites to fluorene intake, absorption and bioavailability of fluorene are highest via oral (dietary) exposure, followed by dermal exposure, and then inhalation exposure (Lao et al., 2018). Animal studies conducted via oral and inhalation exposure also showed that absorption occurs via these routes, as fluorene and/or its hydroxylated metabolites were detected in a dose-related manner in the blood and brain of exposed rats at study termination (Peiffer et al., 2016; Peiffer et al., 2013).

Once absorbed, PAHs are widely distributed to the tissues (ATSDR, 1995). Fluorene was detected in tissue samples obtained from human cadavers at autopsy. Levels of fluorene were highest in abdominal fat > heart > brain > kidney > liver > lung > spleen, suggesting that fluorene, like other PAHs, is widely distributed throughout the body and accumulates preferentially in fatty tissues (Pastor-Belda et al., 2019). Animal studies (short-term inhalation

and subchronic oral and i.p. exposures) in rats detected metabolites of fluorene in the brain, demonstrating that fluorene and fluorene metabolites distribute to the brain (Peiffer et al., 2016; Peiffer et al., 2013).

Across a wide number of studies, PAH metabolites have been detected in all tissue types (ATSDR, 1995). Studies in humans and animals show that fluorene is metabolized to mono-hydroxylated metabolites, including 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene (Gmeiner et al., 2002; Grantham, 1963; Dewhurst, 1962; Neish, 1948). These mono-hydroxylated metabolites have been detected in the urine of humans after oral, inhalation, and/or dermal exposure (Rossbach et al., 2020; Lao et al., 2018; Sochacka-Tatara et al., 2018; Li et al., 2012). Rats exposed via oral, inhalation, or i.p. routes of exposure also produced these metabolites, which were detected in the blood and the brain (Peiffer et al., 2016; Peiffer et al., 2013). A study using rat liver preparations showed that, in addition to 2-OH fluorene, 3-OH fluorene, and 9-OH fluorene, 1-OH fluorene, and 9-fluorenone are generated as metabolites of fluorene after 20 minutes of incubation in vitro; fluorene also reacts with oxygen to form hydroperoxides (IARC, 1983; LaVoie et al., 1981).

PAHs are eliminated via the urine and feces; excretion varies by compound and the route of exposure (Choi et al., 2023; Lao et al., 2018; van Schooten et al., 1997). The amounts of mono-hydroxylated PAH metabolites excreted in the urine decrease as molecular weight increases (ATSDR, 1995). Fluorene is considered a low molecular weight PAH and is excreted primarily in the urine (Lao et al., 2018). A study of human subjects exposed via a PAH-containing lunch showed increased concentrations of mono-hydroxylated fluorene metabolites in the urine soon after exposure (maximum concentrations were reached within 3.8−3.9 hours after exposure); levels approached background within 48 hours (Li et al., 2012). Other human studies showed similar results, with peak urinary levels of metabolites within 1−10 hours of exposure, declining to background levels after 24−48 hours (Rossbach et al., 2020; Fent et al., 2019; Lao et al., 2018). Elimination half-lives for 9-OH fluorene, 3-OH fluorene, and 2-OH fluorene were estimated as 3.1, 6.1, and 2.9 hours, respectively, in one study in which subjects were exposed by diet (Li et al., 2012) and 3.5, 9.3, and 4.8 hours, respectively, in another study in which subjects were exposed primarily by skin contact to fumes (Rossbach et al., 2020).n

3. DERIVATION OF PROVISIONAL VALUES

3.1. DERIVATION OF ORAL REFERENCE DOSES

3.1.1. Derivation of Subchronic Provisional RfD (Subchronic p-RfD)

The database of potentially relevant studies for derivation of an oral subchronic provisional reference value for fluorene is limited to a published, peer-reviewed, 60-day gavage study that evaluated behavioral endpoints in male rats (Peiffer et al., 2016), an unpublished 13-week study that evaluated a comprehensive set of toxicological endpoints in male and female mice (TRL, 1989), and two subchronic to chronic studies in rats with substantial study limitations (Morris et al., 1960; Wilson et al., 1947).

The Peiffer et al. (2016) and TRL (1989) studies identify the liver as a target of toxicity following subchronic oral exposure in rodents. Peiffer et al. (2016) observed biologically significant (>10%), dose-related increases in relative liver weight at ≥10 mg/kg-day in male rats that were also statistically significant ($p < 0.01$). The study did not include investigation of other liver endpoints. Body-weight gain was significantly reduced at 100 mg/kg-day. The focus of the study was a neurobehavioral test battery, which evaluated anxiety, motor activity, and learning and memory; no neurobehavioral or neurotoxic effects relevant to treatment were observed at the tested doses. TRL (1989) observed statistically and biologically (>10%) significant dose-related increases in absolute and relative liver weights in male and female mice at ≥250 mg/kg-day ($p < 0.01$). Relative liver weights in both sexes were found to be statistically significant at 125 mg/kg-day ($p < 0.05$), but the increases at this dose were small (<10%) and not considered biologically significant. Other changes observed at 250 and/or 500 mg/kg-day in this study included enlarged and eosinophilic centrilobular hepatocytes and pigmentation reminiscent of hemosiderin deposition in Kupffer cells (predominantly in males); decreases in RBC count, PCV, and hemoglobin; increased serum total bilirubin and cholesterol and decreased BUN; hemosiderosis and hematopoietic cell proliferation in the spleen; and increased absolute and relative spleen weights. Liver weight was also reportedly increased in rats (sex not specified) exposed to fluorene in the diet at 265.1 mg/kg-day for 104 days (Wilson et al., 1947). A study run in parallel to the 60-day gavage study showed that male rats administered fluorene via i.p. injection at 100 mg/kg-day for 60 days also had biologically and statistically significantly increased relative liver weights (Peiffer et al., 2016).

The Peiffer et al. (2016) and TRL (1989) studies provide dose-response data and, as such, are considered adequate for quantitative toxicity value derivation. The unpublished study by TRL (1989) evaluated a comprehensive set of toxicological endpoints in male and female mice and was used by IRIS to derive a chronic RfD value (U.S. EPA, 1990). However, the NOAEL of 125 mg/kg-day (HEDs = 18.3 and 17.4 mg/kg-day in males and females, respectively) and LOAEL of 250 mg/kg-day (HEDs = 36.6 and 34.7 mg/kg-day in males and females, respectively) identified from this study based on liver, hematological, and splenic effects are 1−2 orders of magnitude higher than the NOAEL of 1 mg/kg-day (HED = 0.2 mg/kg-day) and LOAEL of 10 mg/kg-day (HED = 2.4 mg/kg-day) identified from Peiffer et al. (2016) based on biologically significant increased relative liver weight in male rats. The relative liver weight data from Peiffer et al. (2016) are not suitable for benchmark dose (BMD) modeling because variance data were not presented for the control group. Therefore, a NOAEL (HED) of 0.24 mg/kg-day for increased relative liver weight in the 60-day gavage study by Peiffer et al. (2016) is selected as the point of departure (POD) for derivation of the subchronic p-RfD.

The subchronic p-RfD of 8×10^{-4} mg/kg-day for fluorene is derived by applying a composite uncertainty factor (UF_C) of 300 (reflecting an interspecies uncertainty factor [UF_A] of 3, a database uncertainty factor [UF_D] of 10, and an intraspecies uncertainty factor [UF_H] of 10) to the selected POD of 0.24 mg/kg-day.

Subchronic p-RfD = POD (HED) ÷ UF_C
= 0.24 mg/kg-day ÷ 300
= **8×10^{-4} mg/kg-day**

Table 6 summarizes the uncertainty factors for the subchronic p-RfD for fluorene.

Table 6. Uncertainty Factors for the Subchronic p-RfD for Fluorene

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for uncertainty associated with extrapolating from animals to humans when cross-species dosimetric adjustment (HED calculation) is performed.
UF_D	10	A UF_D of 10 is applied to account for deficiencies in the database. The oral database for fluorene includes an unpublished 13-wk gavage study in male and female mice evaluating a comprehensive set of toxicological endpoints; a 60-d gavage study in male rats that evaluated limited standard toxicological endpoints (body, brain, and liver weights) and performed an extensive neurobehavioral test battery evaluating anxiety, motor activity, and learning and memory; and two subchronic to chronic studies in rats with reporting deficiencies (Morris et al., 1960; Wilson et al., 1947). No studies of reproductive or developmental toxicity were located; however, for PAHs with larger databases, reproductive and/or developmental effects have been reported (U.S. EPA, 2017; EC, 2002; ATSDR, 1995).
UF_H	10	A UF_H of 10 is applied to account for interindividual variability, in the absence of information to assess toxicokinetic and toxicodynamic variability of fluorene in humans. As the critical effect in the principal study was only examined in male rats, it is unclear how these effects may inform sex-specific human variability and susceptibility.
UF_L	1	A UF_L of 1 is applied because the POD is a NOAEL.
UF_S	1	A UF_S of 1 is applied because the subchronic POD was derived from subchronic data.
UF_C	300	Composite UF = $UF_A \times UF_D \times UF_H \times UF_L \times UF_S$.

HED = human equivalent dose; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; p-RfD = provisional reference dose; PAH = polycyclic aromatic hydrocarbons; POD = point of departure; UF = uncertainty factor; UF_A = interspecies uncertainty factor; UF_C = composite uncertainty factor; UF_D = database uncertainty factor; UF_H = intraspecies uncertainty factor; UF_L = LOAEL-to-NOAEL uncertainty factor; UF_S = subchronic-to-chronic uncertainty factor.

Confidence in the subchronic p-RfD for fluorene is low, as described in Table 7.

Table 7. Confidence Descriptors for the Subchronic p-RfD for Fluorene

Confidence Categories	Designation	Discussion
Confidence in study	M	Confidence in the principal study (Peiffer et al., 2016) is medium. The study examined a limited number of standard toxicological endpoints (i.e., body, brain, and liver weights) in male rats after 60 d of gavage exposure. However, an extensive neurobehavioral test battery was performed and three exposure levels were evaluated, permitting the identification of both a NOAEL (at the lowest dose) and a LOAEL (at the mid dose).
Confidence in database	L	Confidence in the database is low. The oral database for fluorene includes an unpublished 13-wk gavage study in male and female mice evaluating a comprehensive set of toxicological endpoints; a 60-d gavage study in male rats that evaluated limited standard toxicological endpoints (body, brain, and liver weights) and performed an extensive neurobehavioral test battery evaluating anxiety, motor activity, and learning and memory; and two subchronic to chronic studies in rats with reporting deficiencies (Morris et al., 1960; Wilson et al., 1947). No studies of reproductive or developmental toxicity were located; however, for PAHs with larger databases, reproductive and/or developmental effects have been reported (U.S. EPA, 2017; EC, 2002; ATSDR, 1995).
Confidence in subchronic p-RfD[a]	L	Overall confidence in the subchronic p-RfD is low.

[a]The overall confidence cannot be greater than the lowest entry in the table.

L = low; LOAEL = lowest-observed-adverse-effect level; M = medium; NOAEL = no-observed-adverse-effect level; PAH = polycyclic aromatic hydrocarbon; p-RfD = provisional reference concentration.

3.1.2. Derivation of Chronic Provisional RfD (Chronic p-RfD)

A chronic p-RfD value was not derived because an oral RfD value is available on the U.S. EPA's IRIS database (U.S. EPA, 1990).

3.2. DERIVATION OF INHALATION REFERENCE CONCENTRATIONS

No subchronic or chronic provisional reference concentration (p-RfC) values can be derived because the database of fluorene inhalation studies is limited to a 14-day study that evaluated only behavioral effects in fluorene-exposed rats (Peiffer et al., 2013). As detailed in Appendix A, the application of an alternate analogue approach was attempted but screening p-RfCs could not be derived for fluorene because no candidate analogues with inhalation toxicity values were identified.

3.3. SUMMARY OF NONCANCER PROVISIONAL REFERENCE VALUES

Table 8 presents a summary of noncancer references values.

Table 8. Summary of Noncancer Reference Values for Fluorene (CASRN 86-73-7)

Toxicity Type (Units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD (HED/HEC)	UF_C	Principal Study
Subchronic p-RfD (mg/kg-d)	Rat/M	Increased relative liver weight	8×10^{-4}	NOAEL	0.24	300	Peiffer et al. (2016)
Chronic p-RfD (mg/kg-d)	An oral RfD of 0.04 mg/kg-d is available on IRIS (U.S. EPA, 1990).						
Subchronic p-RfC (mg/m^3)	NDr						
Chronic p-RfC (mg/m^3)	NDr						

HEC = human equivalent concentration; HED = human equivalent dose; IRIS = Integrated Risk Information System; M = male(s); NDr = not determined; NOAEL = no-observed-adverse-effect level; POD = point of departure; p-RfC = provisional reference concentration; p-RfD = provisional reference dose; RfD = reference dose; UF_C = composite uncertainty factor.

3.4. CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR AND PROVISIONAL CANCER RISK ESTIMATES

A cancer assessment was not performed because a cancer weight-of-evidence (WOE) is available on the U.S. EPA's IRIS database (U.S. EPA, 1990), which characterized fluorene as Group D, not classifiable as to human carcinogenicity (based on no human data and inadequate data from animal bioassays). No newer cancer data were identified.

APPENDIX A. SCREENING PROVISIONAL VALUES

Due to the lack of evidence described in the main Provisional Peer-Reviewed Toxicity Value (PPRTV) assessment, it is inappropriate to derive provisional inhalation toxicity values for fluorene. However, some information is available for this chemical, which although insufficient to support derivation of a provisional toxicity value under current guidelines, may be of limited use to risk assessors. In such cases, the Center for Public Health and Environmental Assessment (CPHEA) summarizes available information in an appendix and develops a "screening value." Appendices receive the same level of internal and external scientific peer review as the provisional reference values to ensure their appropriateness within the limitations detailed in the document. Users of screening toxicity values in an appendix to a PPRTV assessment should understand that there could be more uncertainty associated with deriving an appendix screening toxicity value than for a value presented in the body of the assessment. Questions or concerns about the appropriate use of screening values should be directed to the CPHEA.

APPLICATION OF AN ALTERNATIVE ANALOGUE APPROACH (METHODS)

The analogue approach allows for the use of data from related compounds to calculate screening values when data for the compound of interest are limited or unavailable. Details regarding searches and methods for analogue analysis are presented in Wang et al. (2012) and Lizarraga et al. (2023). Three types of potential analogues (structural, metabolic, and toxicity-like) are identified to facilitate the final analogue chemical selection. The analogue approach may or may not be route specific or applicable to multiple routes of exposure. All information is considered together as part of the final weight-of-evidence (WOE) approach to select the most suitable analogue both toxicologically and chemically.

An expanded analogue identification approach was developed to collect a more comprehensive set of candidate analogues for the compounds undergoing U.S. Environmental Protection Agency (U.S. EPA) PPRTV screening-level assessment. As described below, this method includes application of a variety of tools and methods for identifying candidate analogues that are similar to the target chemical based on chemical structure and key features; metabolic relationships; or related toxic effects and mechanisms of action.

To identify structurally-related compounds, an initial pool of analogues is identified using automated tools, including ChemIDplus[11] (NLM, 2021), CompTox Chemicals Dashboard (U.S. EPA, 2021b), and Organisation for Economic Co-operation and Development (OECD) Quantitative Structure-Activity Relationship (QSAR) Toolbox (OECD, 2020), to conduct structural similarity searches. Additional analogues identified as ChemIDplus-related substances, parent, salts and mixtures, and CompTox-related substances are considered. CompTox Generalized Read-Across (GenRA) analogues are collected using the methods available on the publicly available GenRA Beta version, which may include Morgan fingerprints, Torsion fingerprints, ToxPrints and ToxCast, Tox21, and ToxRef data. For compounds that have very few analogues identified by structure similarity using a similarity threshold of 0.8 or 80%, substructure searches in the QSAR Toolbox may be performed, or similarity searches may be re-run using a reduced similarity threshold (e.g., 70 or 60%). The compiled list of candidate analogues is batch run through the CompTox Chemicals Dashboard where QSAR-ready

[11]National Library of Medicine (NLM) retired ChemIDplus in December 2022.

simplified molecular-input line-entry system (SMILES) notations are collected and toxicity data availability is determined (e.g., from the Agency for Toxic Substances and Disease Registry [ATSDR], Office of Environmental Health Hazard Assessment [OEHHA], California Environmental Protection Agency [CalEPA], U.S. EPA Integrated Risk Information System [IRIS], PPRTV assessments). The batch output information is then uploaded into the Chemical Assessment Clustering Engine (ChemACE) (U.S. EPA, 2011a), which clusters the chemicals based on chemical fragments and displays the toxicity data availability for each candidate. The ChemACE output is reviewed by an experienced chemist, who narrows the list of structural analogues based on known or expected structure-toxicity relationships, reactivity, and known or expected metabolic pathways.

Toxicokinetic studies tagged as potentially relevant supplemental material during screening were used to identify metabolic analogues (metabolites and metabolic precursors). Metabolites were also identified from the two OECD QSAR Toolbox metabolism simulators (in vivo rat metabolism simulator and rat liver S9 metabolism simulator). Targeted PubMed searches were conducted to identify metabolic precursors and other compounds that share any of the observed or predicted metabolites identified for the target chemical. Metabolic analogues are then added to the pool of candidate analogues and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, U.S. EPA IRIS, PPRTV assessments).

In vivo toxicity data for the target chemical (if available) are evaluated to determine whether characteristic effects associated with a particular mechanism of toxicity was observed (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation). In addition, in vitro mechanistic data tagged as potentially relevant supplemental material during screening or obtained from tools including GenRA, ToxCast/Tox21, and Comparative Toxicogenomics Database (CTD) (CTD, 2022; Davis et al., 2021) were evaluated for this purpose. Data from CompTox Chemicals Dashboard ToxCast/Tox21 are collected to determine bioactivity of the target chemical in in vitro assays that may indicate potential mechanism(s) of action. The GenRA option within the Dashboard also offers an option to search for analogues based on similarities in activity in ToxCast/Tox21 in vitro assays. Using the ToxCast/Tox21 bioactivity data, nearest neighbors identified with similarity indices of ≥0.5 may be considered potential candidate analogues. The CTD (CTD, 2022; Davis et al., 2021) is searched to identify compounds with gene interactions similar to interactions induced by the target chemical; compounds with gene interactions similar to the target chemical (with a similarity index >0.5) may be considered potential candidate analogues. These compounds are then added to the pool of candidate analogues and toxicity data availability is determined (e.g., from ATSDR, OEHHA, CalEPA, U.S. EPA IRIS, PPRTV assessments).

The application of a variety of different tools and methods to identify candidate analogues serves to minimize the limitations of any individual tool with respect to the pool of chemicals included, chemical fragments considered, and methods for assessing similarity. Further, the inclusion of techniques to identify analogues based on metabolism and toxicity or bioactivity expands the pool of candidates beyond those based exclusively on structural similarity. The specific tools described above used for the expanded analogue approach searches were selected because they are publicly available, supported by U.S. and OECD agencies, updated regularly, and widely used.

Analogue Search Results for Fluorene

Candidate analogues for fluorene were identified based on metabolic relationships, structural relationships, and toxicity/mechanisms/mode-of-action (MOA) relationships. For candidates identified through these approaches, the U.S. EPA (IRIS and PPRTV assessments), ATSDR, and CalEPA sources were searched for subchronic, intermediate, and chronic inhalation toxicity values. No candidate analogues with inhalation toxicity values were identified. Details are provided below.

Identification of Structural Analogues with Established Toxicity Values

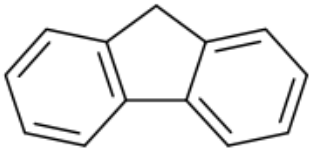
Fluorene is not a member of an existing OECD or New Chemical category. Candidate structural analogues for fluorene were identified using similarity searches in the OECD Toolbox, the U.S. EPA CompTox Chemicals Dashboard, and ChemIDplus tools. A total of 210 unique structural analogues were identified for fluorene in the Dashboard, OECD QSAR Toolbox, and ChemIDplus (80% similarity threshold).

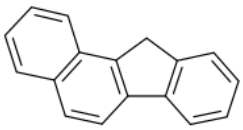
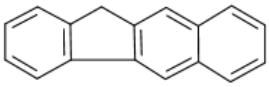
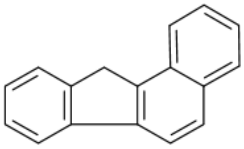
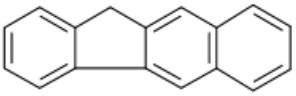
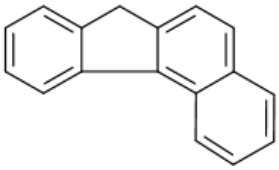
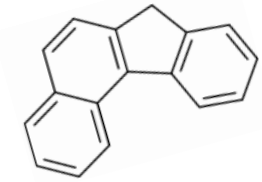
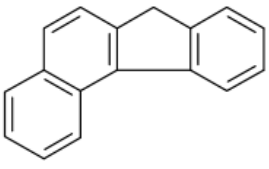
The list of potential analogues was reviewed by a chemist with expertise in read-across. Criteria for including candidates were as follows:

- Includes one, and only one, five-membered ring.
- Includes no fewer than two, and no more than three, aromatic rings.
- Does not include any ring substitutions.
- Deuterated compounds are excluded because the toxicokinetics may differ relative to compounds that are not deuterated.

Using these criteria, a total of seven candidate structural analogues for fluorene were identified, as shown in Table A-1; all structural analogues are benzofluorenes. Two CASRNs (benzo[*a*]fluorene, CASRN 30777-18-5 and benzo[*c*]fluorene, CASRN 30777-20-9) identified as analogues by the tools appear to represent general structures (systematic names indicating the location of the hydrogen could not be verified with readily available sources). However, for completeness, the names and CASRNs were included in searches for toxicity values.

Table A-1. Candidate Structural Analogues Identified for Fluorene based on Tools and Expert Judgment



Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches	Structure
Dashboard (Tanimoto), OECD Toolbox (Dice), and ChemIDplus (method not described)	11H-Benzo[*a*]fluorene (CASRN 238-84-6)	
	11H-Benzo[*b*]fluorene (CASRN 243-17-4)	
OECD Toolbox (Dice), and ChemIDplus (method not described)	Benzo[*a*]fluorene (CASRN 30777-18-5)	
	Benzo[*b*]fluorene (CASRN 30777-19-6)	
Dashboard (Tanimoto) and ChemIDplus (method not described)	7H-Benzo[*c*]fluorene (CASRN 205-12-9)	
ChemIDplus (method not described)	Benzo[*c*]fluorene (CASRN 30777-20-9)	
	Benzofluorene (CASRN 61089-87-0)	

[a]80% similarity threshold was applied.

OECD = Organisation for Economic Co-operation and Development.

No inhalation toxicity values were identified for any of the candidate structural analogues.

Identification of Toxicokinetic Precursors or Metabolites with Established Toxicity Values

Metabolites of fluorene identified via incubation with rat liver microsomes include 9-hydroxyfluorene (9-fluorenol), 1-hydroxyfluorene, 9-ketofluorene (9-fluorenone), and hydroperoxides (IARC, 1983). Predicted metabolites were collected from the OECD QSAR Toolbox. PubMed searches (searching "fluorene" or "86-73-7" and "metabolite") were conducted to identify metabolic precursors to fluorene. No metabolic precursors were identified. PubMed was also searched to identify other compounds that are metabolized to any of the observed or predicted metabolites of fluorene (searching the metabolite name or [CASRN if available] and "metabolite"). No compounds that share at least one metabolite with fluorene were identified in these searches.

Table A-2 summarizes the 12 candidate metabolic analogues for fluorene (4 observed metabolites and an additional 8 unique predicted metabolites). Searches for relevant toxicity values for the candidate metabolic analogues of fluorene did not identify inhalation toxicity values for any of the observed or predicted metabolites.

Table A-2. Candidate Metabolic Analogues of Fluorene

Relationship to Fluorene	Compound
Metabolic precursor	None identified
Metabolite	9-Fluorenol (CASRN 1689-64-1)
	1-Hydroxyfluorene (CASRN 6344-61-2)
	9-Ketofluorene (9-fluorenone, CASRN 486-25-9)
	Hydroperoxides[a]
	3-hydroxyfluorene (CASRN 6344-67-8)
	2-hydroxyfluorene (CASRN 2443-58-5)
	9H-fluoren-4-ol (CASRN 28147-35-5)
	9H-fluorene-2,9-diol (CASRN 106593-45-7)
	9H-fluorene-2,3-diol[a]
	9H-fluorene-3,4-diol (CASRN 42523-20-6)
	9H-fluorene-1,2-diol (CASRN 42523-11-5)
	9H-fluorene-3,9-diol (CASRN 1381944-22-4)
Shares common metabolite(s)	None identified

[a]CASRN not available for this metabolite.

Identification of Analogues on the Basis of Toxicity/Mechanistic/MOA Information and Established Toxicity Values

Available toxicity and mechanistic data for fluorene were evaluated to determine whether these data could be used to identify candidate analogues. Animal studies on the toxicity of

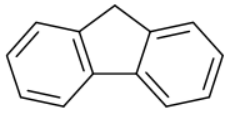
fluorene identified through the literature searches were reviewed to determine whether there were in vivo toxicity data demonstrating characteristic effects associated with a specific mechanism of toxicity (e.g., cholinesterase inhibition, inhibition of oxidative phosphorylation) that could be used to identify candidate analogues. Studies of fluorene exposure by oral administration (Peiffer et al., 2016; TRL, 1989) reported liver and spleen effects and hematology changes, while a short-term inhalation study (Peiffer et al., 2013) reported a lack of toxicologically relevant neurobehavioral changes. None of these oral or inhalation studies indicated a specific mechanism of toxicity that could be used to identify candidate analogues.

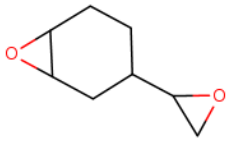
Fluorene was active in 28 ToxCast/Tox21, 6 EDSP21, and 9 PubChem bioactivity assays reported in the Dashboard (invitrodb version 3.3; U.S. EPA, 2020a; U.S. EPA, 2020b). The GenRA option within the Dashboard offers an option to search for analogues based on similarities in activity in ToxCast/Tox21 in vitro assays. Using the ToxCast bioactivity data, none of the nearest neighbors identified by GenRA had similarity indices ≥0.5 (the highest index was 0.22 for carbamazepine). Using the Tox21 bioactivity data, only one of the nearest neighbors identified by GenRA had a similarity index of at least 0.5: 4-vinyl-1-cyclohexene dioxide (similarity index = 0.53) (U.S. EPA, 2020c). This compound does not have an inhalation toxicity value from the U.S. EPA (IRIS and PPRTV assessments), ATSDR, or CalEPA.

The CTD identified several compounds with gene interactions similar to interactions induced by fluorene. In the CTD, similarity is measured by the Jaccard index, calculated as the size of the intersection of interacting genes for chemical A and chemical B divided by the size of the union of those genes (range 0 [no similarity] to 1 [complete similarity]). Among the compounds with gene interactions similar to fluorene, the numbers of common gene interactions ranged from 3 to 7 and similarity indices ranged from 0.19 to 0.27; the compound with the highest similarity index (0.27) was sudan III (CASRN 85-86-9). There were no compounds with a similarity index ≥0.5.

The methods outlined above identified only 4-vinyl-1-cyclohexene dioxide as a candidate mechanistic analogue for fluorene, as shown in Table A-3. However, 4-vinyl-1-cyclohexene dioxide does not have an inhalation toxicity value.

Table A-3. Candidate Mechanistic Analogues Identified for Fluorene



Tool (method)[a]	Analogue (CASRNs) Selected for Toxicity Value Searches	Structure
GenRA (Beta), Biology: Tox21 data	4-Vinyl-1-cyclohexene dioxide (CASRN 106-87-6)	

[a]50% similarity threshold was applied.

GenRA = Generalized Read-Across.

Summary

Searches for metabolic, structural, and toxicity/mechanistic analogues for fluorene yielded a total of 20 unique candidate analogues: 12 metabolites, 7 structural analogues[12], and 1 mechanistic analogue. None of the candidate analogues have inhalation toxicity values from the U.S. EPA, ATSDR, or CalEPA. Therefore, no suitable candidate analogues were identified to calculate screening inhalation provisional toxicity values.

INHALATION NONCANCER TOXICITY VALUES

Derivation of a Screening Subchronic and Chronic Provisional Reference Concentrations (p-RfCs)

Subchronic and chronic p-RfCs could not be derived due to the lack of an appropriate analogue having inhalation toxicity values.

[12]Although seven unique CASRNs were retrieved during structural similarity searches, two of the CASRNs for structural analogues appear to represent general structures.

APPENDIX B. DATA TABLES

Table B-1. Effects in Male Wistar Rats Treated with Fluorene via Gavage for 60 Days[a]

ADD [HED] in mg/kg-d				
Endpoint	**0 [0]**	**1 [0.24]**	**10 [2.4]**	**100 [23.6]**
Number evaluated (*n*)	8	8	8	8
Body-weight gain (% compared to Day 1)				
Day 2	0.60[b,c]	0.35 (+0%)	−0.14 (−1%)	−3.10 (−4%)**
Day 7	2.32	1.83 (+0%)	1.34 (−1%)	−5.56 (−8%)**
Day 14	7.25	7.25 (+0%)	7.25 (+0%)	0.35 (−7%)**
Day 21	12.92	12.43 (+0%)	11.69 (−1%)	5.28 (−8%)**
Day 28	17.61	17.11 (+0%)	16.62 (−1%)	10.21 (−7%)**
Relative liver weight (% body weight)	2.69[b,d]	2.84 (+6%)*	3.16 (+17%)**	3.69 (+37%)**

[a]Peiffer et al. (2016).
[b]Data are means based on graphically reported data extracted using the MATLAB tool GRABIT; variance values were not extracted.
[c]Value in parentheses is % change relative to control = control mean − treatment mean (for data reported as %).
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control at ($p < 0.05$) by Dunnett t-test, as reported by the study authors.
**Significantly different from control at ($p < 0.01$) by Dunnett t-test, as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose.

Table B-2. Select Clinical Signs of Toxicity in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]

Males: ADD [HED] in mg/kg-d				
Effect	**0 [0]**	**125 [18.3]**	**250 [36.6]**	**500 [73.7]**
	Males			
Salivation	1/20 (5%)[b]	16/20 (80%)*	14/20 (70%)*	19/20 (95%)*
Hypoactivity	1/20 (5%)	2/20 (10%)	3/20 (15%)	17/20 (85%)*
Labored respiration	0/20 (0%)	0/20 (0%)	0/20 (0%)	3/20 (15%)
Ptosis	0/20 (0%)	1/20 (5%)	0/20 (0%)	4/20 (20%)
Urine wet abdomen	0/20 (0%)	1/20 (5%)	2/20 (10%)	3/20 (15%)
Unkempt appearance	0/20 (0%)	3/20 (15%)	0/20 (0%)	4/40 (20%)
Females: ADD [HED] in mg/kg-d				
	0 [0]	**125 [17.4]**	**250 [34.7]**	**500 [70.1][c]**
Salivation	1/20 (5%)	11/20 (55%)*	14/20 (70%)*	16/20 (80%)*
Hypoactivity	2/10 (10%)	1/20 (5%)	1/20 (5%)	15/20 (75%)*
Labored respiration	0/20 (0%)	0/20 (0%)	0/20 (0%)	3/20 (15%)
Ptosis	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)
Urine wet abdomen	0/20 (0%)	0/20 (0%)	0/20 (0%)	0/20 (0%)
Unkempt appearance	0/20 (0%)	1/20 (5%)	0/20 (0%)	2/20 (10%)

[a]TRL (1989).
[b]Number affected/number examined (% incidence).
[c]Two 500 mg/kg-day females (194 and 195) died during week 1 and were replaced with animals from the satellite group (199S and 200S); 194/199S and 195/200S were counted as single animals for the purpose of tabulating incidence data.
*Statistically significant from control ($p < 0.05$) based on one-tailed Fisher's exact test performed for this review.

ADD = adjusted daily dose; HED = human equivalent dose.

Table B-3. Food Consumption on Select Weeks in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]

Males: ADD [HED] in mg/kg-d				
Endpoint	**0 [0]**	**125 [18.3]**	**250 [36.6]**	**500 [73.7]**
Food consumption (g/animal/week)				
Week 1	30.5 ± 3.29[b,c]	34.2 ± 2.76 (+12%)*	33.6 ± 4.64 (+10%)	31.2 ± 5.26 (+2%)
Week 2	29.1 ± 4.02	32.2 ± 2.92 (+11%)*	35.3 ± 7.18 (+21%)**	33.6 ± 4.84 (+15%)**
Week 3	28.4 ± 3.72	30.9 ± 1.89 (+9%)*	32.3 ± 4.54 (+14%)*	31.9 ± 2.72 (+12%)**
Week 6	30.5 ± 2.60	31.6 ± 2.10 (+4%)	32.9 ± 2.64 (+8%)*	33.8 ± 2.86 (+11%)**
Week 8	31.5 ± 3.21	32.7 ± 1.89 (+4%)	32.2 ± 3.09 (+2%)	37.7 ± 2.41 (+20%)**
Week 9	29.4 ± 3.88	32.2 ± 2.11 (+10%)*	35.9 ± 3.18 (+22%)**	32.0 ± 2.79 (+9%)*
Week 10	31.6 ± 2.83	32.3 ± 1.87 (+2%)	34.8 ± 2.91 (+10%)**	35.0 ± 2.59 (+11%)**
Week 11	28.7 ± 2.53	30.3 ± 2.08 (+6%)	32.5 ± 2.93 (+13%)**	31.9 ± 2.57(+11%)**
Week 12	31.0 ± 2.31	32.5 ± 2.16(+5%)	34.1 ± 2.29 (+10%)**	34.3 ± 2.85 (+11%)**
Week 13	25.7 ± 2.61	26.7 ± 1.29 (+4%)	28.3 ± 3.51 (+10%)*	28.0 ± 2.98 (+9%)
Females: ADD[HED] in mg/kg-d				
	0 [0]	**125 [17.4]**	**250 [34.7]**	**500 [70.1]**
Food consumption (g/animal/week)				
Week 1	27.6 ± 2.16	27.5 ± 2.55 (+0%)	29.3 ± 3.20 (+6%)	31.8 ± 4.67 (+15%)**
Week 2	28.0 ± 2.02	30.0 ± 3.91 (+7%)	31.6 ± 3.28 (+13%)**	33.3 ± 4.26 (+19%)**
Week 3	29.5 ± 2.48	28.7 ± 2.28 (−3%)	29.3 ± 2.38 (−1%)	31.8 ± 2.53 (+8%)*
Week 6	30.3 ± 2.08	31.7 ± 2.43 (+5%)	30.8 ± 2.51 (+2%)	34.8 ± 6.55(+15%)*
Week 8	30.9 ± 3.08	31.4 ± 2.95 (+2%)	32.0 ± 2.52 (+4%)	33.6 ± 3.68 (+9%)*
Week 9	29.8 ± 3.42	31.7 ± 3.43 (+6%)	31.8 ± 2.49 (+7%)	32.9 ± 3.03 (+10%)*
Week 10	31.7 ± 2.80	31.7 ± 2.63 (+0%)	33.2 ± 2.96 (+5%)	34.1 ± 2.38 (+8%)*
Week 11	29.5 ± 3.57	29.6 ± 2.63 (+0%)	31.1 ± 2.77 (+5%)	31.5 ± 1.88 (+7%)
Week 12	31.6 ± 2.88	31.3 ± 2.24 (−1%)	33.8 ± 3.16 (+7%)*	34.4 ± 2.17 (+9%)**
Week 13	26.5 ± 2.99	26.2 ± 2.01 (−1%)	27.2 ± 2.13 (+3%)	28.1 ± 2.19 (+6%)

[a]TRL (1989).
[b]Data are means ± SD.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Dunnett's test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Dunnett's test ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation.

Table B-4. Body-Weight Effects on Select Weeks in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]

Males: ADD [HED] in mg/kg-d				
Endpoint	**0 [0]**	**125 [18.3]**	**250 [36.6]**	**500 [73.7]**
Body weight (g)				
Week 1	28.8 ± 2.87[b,c]	29.8 ± 1.72 (+3%)	29.7 ± 1.88 (+3%)	28.9 ± 2.09 (+0%)
Week 2	29.9 ± 2.76	30.2 ± 1.85 (+1%)	30.1 ± 1.83 (+1%)	30.1 ± 1.46 (+1%)
Week 5	31.7 ± 3.17	32.5 ± 1.63 (+3%)	32.7 ± 1.84 (+3%)	32.5 ± 1.69 (+3%)
Week 6	31.8 ± 3.11	32.5 ± 1.81 (+2%)	32.7 ± 1.70 (+3%)	33.2 ± 1.57 (+4%)
Week 7	32.2 ± 3.15	33.0 ± 1.71 (+2%)	33.2 ± 1.85 (+3%)	33.7 ± 1.69 (+5%)
Week 9	32.7 ± 3.22	33.3 ± 1.81 (+2%)	33.5 ± 1.95 (+2%)	34.3 ± 1.76 (+5%)
Week 10	33.2 ± 3.33	33.5 ± 1.72 (+1%)	33.9 ± 2.04 (+2%)	34.5 ± 1.79 (+4%)
Week 11	33.7 ± 3.38	34.2 ± 1.79 (+1%)	34.4 ± 2.19 (+2%)	35.0 ± 1.87 (+4%)
Week 12	33.7 ± 3.32	34.2 ± 1.88 (+1%)	34.0 ± 2.81 (+1%)	34.7 ± 1.91 (+3%)
Week 13	33.7 ± 3.24	34.3 ± 1.86 (+2%)	34.5 ± 2.11 (+2%)	34.8 ± 2.30 (+3%)
Body-weight change (Weeks 1−13)[d] (g)	4.9	4.5 (−8%)	4.8 (−2%)	5.9 (+20%)
Females: ADD [HED] in mg/kg-d				
	0 [0]	**125 [17.4]**	**250 [34.7]**	**500 [70.1]**
Body weight (g)				
Week 1	23.2 ± 1.80	23.6 ± 1.57 (+2%)	23.3 ± 1.24 (+0%)	23.8 ± 2.17 (+3%)
Week 2	23.6 ± 1.73	24.3 ± 1.36 (+3%)	24.1 ± 1.59 (+2%)	25.1 ± 2.01 (+6%)*
Week 5	25.6 ± 1.84	26.1 ± 1.76 (+2%)	26.3 ± 1.80 (+3%)	27.6 ± 2.11 (+8%)**
Week 6	25.7 ± 2.12	26.2 ± 1.44 (+2%)	26.2 ± 1.55 (+2%)	27.6 ± 1.97 (+7%)**
Week 7	26.2 ± 1.99	26.4 ± 1.33 (+1%)	26.6 ± 1.59 (+2%)	27.8 ± 2.09 (+6%)*
Week 9	26.3 ± 2.00	27.1 ± 1.68 (+3%)	27.1 ± 1.58 (+3%)	28.3 ± 1.83 (+8%)**
Week 10	27.2 ± 2.31	27.0 ± 1.39 (−1%)	27.2 ± 1.68 (+0%)	28.7 ± 2.22 (+6%)*
Week 11	27.5 ± 2.40	27.6 ± 1.74 (+0%)	27.9 ± 1.89 (+1%)	29.4 ± 1.96 (+7%)*
Week 12	27.2 ± 2.10	27.2 ± 1.68 (+0%)	27.8 ± 1.95 (+2%)	29.2 ± 1.98 (+7%)**
Week 13	27.6 ± 1.97	27.5 ± 1.44 (+0%)	28.1 ± 1.88 (+2%)	29.5 ± 1.94 (+7%)**
Body-weight change (Weeks 1−13)[d] (g)	4.4	3.9 (−11%)	4.8 (+9%)	5.7 (+30%)

[a]TRL (1989).
[b]Data are means ± SD.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Body-weight change calculated for this review as mean body weight at week 13 − mean body weight at Week 1.
*Significantly different from control by Dunnett's test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Dunnett's test ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation.

Table B-5. Select Hematological Effects in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]

Males: ADD [HED] in mg/kg-d				
Endpoint	**0 [0]**	**125 [18.3]**	**250 [36.6]**	**500 [73.7]**
Number evaluated (*n*)	9[b]	10	10	10
RBC count ($\times 10^6$)/µL	8.23 ± 0.53[c,d]	7.68 ± 0.77 (−7%)	7.52 ± 0.54 (−9%)	6.47 ± 0.65 (−21%)**
PCV (%)	43.9 ± 3.60	41.4 ± 3.85 (−6%)	39.7 ± 3.66 (−10%)*	34.4 ± 3.41 (−22%)**
Hemoglobin (g/dL)	13.4 ± 0.71	13.4 ± 0.79 (+0%)	12.9 ± 0.52 (−4%)	11.3 ± 0.90 (−16%)**
MCV (fL)	53.8 ± 2.6	54.3 ± 0.9 (+1%)	53.2 ± 1.8 (−1%)	53.7 ± 0.7 (+0%)
MCH (pg)	16.3 ± 0.75	17.6 ± 0.94 (+8%)**	17.2 ± 0.90 (+6%)	17.5 ± 0.81 (+7%)*
MCHC (g/dL)	30.6 ± 1.78	32.5 ± 1.51 (+6%)	32.6 ± 2.05 (+7%)*	33.0 ± 1.40 (+8%)*
WBC count ($\times 10^3$/µL)	7.0 ± 2.37	6.8 ± 1.54 (−3%)	6.2 ± 1.56 (−11%)	7.8 ± 3.03 (+11%)
Females: ADD [HED] in mg/kg-d				
	0 [0]	**125 [17.4]**	**250 [34.7]**	**500 [70.1]**
Number evaluated (*n*)	10	10	10	10
RBC count ($\times 10^6$)/µL	8.35 ± 0.54	8.01 ± 0.73 (−4%)	7.52 ± 0.43 (−10%)*	6.86 ± 0.83 (−18%)**
PCV (%)	45.2 ± 2.85	43.9 ± 5.07 (−3%)	40.7 ± 2.68 (−10%)*	36.8 ± 2.66 (−19%)**
Hemoglobin (g/dL)	14.2 ± 0.69	14.0 ± 1.01 (−1%)	13.6 ± 0.68 (−4%)	12.4 ± 0.90 (−13%)**
MCV (fL)	54.5 ± 1.1	55.1 ± 1.7 (+1%)	54.7 ± 1.2 (+0%)	56.3 ± 1.3 (+3%)*
MCH (pg)	17.0 ± 0.67	17.5 ± 0.72 (+3%)	18.1 ± 0.98 (+6%)*	18.3 ± 2.32 (+8%)
MCHC (g/dL)	31.4 ± 1.19	32.1 ± 1.76 (+2%)	33.4 ± 1.70 (+6%)*	33.8 ± 1.20 (+8%)**
WBC count ($\times 10^3$/µL)	6.3 ± 2.46	7.0 ± 1.90 (+11%)	7.1 ± 1.69 (+13%)	9.2 ± 3.62 (+46%)*

[a]TRL (1989).
[b]One specimen clotted and was not used for analysis.
[c]Data are means ± SD.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Dunnett's test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Dunnett's test ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; MCH = mean corpuscular hemoglobin; MCHC = mean corpuscular hemoglobin concentration; MCV = mean corpuscular volume; PCV = packed cell volume; RBC = red blood cell; SD = standard deviation; WBC = white blood cell.

Table B-6. Select Clinical Chemistry Effects in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]

Males: ADD [HED] in mg/kg-d				
Endpoint	**0 [0]**	**125 [18.3]**	**250 [36.6]**	**500 [73.7]**
Number evaluated (*n*)	9[b]	10	10	10
Cholesterol (mg/dL)	139.9 ± 23.87[c,d]	148.9 ± 13.12 (+6%)	175.5 ± 27.32 (+25%)**	174.4 ± 22.89 (+25%)**
BUN (mg/dL)	24.6 ± 4.08[#]	20.4 ± 2.75 (−17%)	19.7 ± 5.32 (−20%)*	19.2 ± 4.11 (−22%)*
Total bilirubin (mg/dL)	0.28 ± 0.10[#]	0.20 ± 0.10 (−29%)	0.33 ± 0.10 (+18%)	0.45 ± 0.09 (+61%)**
ALP (U/L)	38.8 ± 10.18	43.9 ± 17.07 (+13%)	43.5 ± 38.64 (+12%)	36.3 ± 16.56 (−6%)
ALT (U/L)	24.0 ± 6.10	20.6 ± 5.22 (−14%)	21.4 ± 5.27 (−11%)	25.6 ± 14.66 (+7%)
AST (U/L)	72.2 ± 30.25	43.7 ± 6.21 (−39%)	56.1 ± 21.44 (−22%)	50.2 ± 14.10 (−30%)
LDH (U/L)	121.9 ± 88.44	84.3 ± 21.92 (−31%)	84.5 ± 26.98 (−31%)	89.1 ± 47.70 (−27%)
Potassium (meq/L)	10.12 ± 1.12	9.86 ± 1.35 (−3%)	10.07 ± 1.50 (+0%)	8.76 ± 0.84 (−13%)
	Females: ADD [HED] in mg/kg-d			
	0 [0]	**125 [17.4]**	**250 [34.7]**	**500 [70.1]**
Number evaluated (*n*)	10	9[b]	10	9[b]
Cholesterol (mg/dL)	104.2 ± 27.38	124.8 ± 32.17 (+20%)	143.6 ± 25.34 (+38%)*	162.4 ± 33.22 (+56%)**
BUN (mg/dL)	20.1 ± 5.10[#]	17.0 ± 2.42 (−15%)	17.0 ± 3.19 (−15%)	15.3 ± 1.65 (−24%)*
Total bilirubin (mg/dL)	0.21 ± 0.10[#]	0.23 ± 0.11 (+10%)	0.27 ± 0.12 (+29%)	0.36 ± 0.08 (+71%)*
ALP (U/L)	54.9 ± 10.00	43.0 ± 10.18 (−22%)*	47.2 ± 8.66 (−14%)	39.1 ± 8.99 (−29%)**
ALT (U/L)	19.1 ± 4.40	19.4 ± 3.13 (+2%)	21.8 ± 5.59 (+14%)	24.9 ± 5.16 (+30%)*
AST (U/L)	60.6 ± 20.72	53.3 ± 12.50 (−12%)	56.8 ± 15.93 (−6%)	55.5 ± 10.48 (−8%)
LDH (U/L)	122.6 ± 56.72	100.7 ± 17.18 (−18%)	89.8 ± 31.64 (−27%)	86.0 ± 36.52 (−30%)
Potassium (meq/L)	10.00 ± 0.95	9.57 ± 1.01 (−4%)	9.41 ± 0.64 (−6%)	8.65 ± 0.95 (−14%)**

[a]TRL (1989).
[b]A specimen could not be obtained from one animal.
[c]Data are means ± SD.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
*Significantly different from control by Dunnett's test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Dunnett's test ($p < 0.01$), as reported by the study authors.
[#]Significant trend test (not further specified; $p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; HED = human equivalent dose; LDH = lactate dehydrogenase; SD = standard deviation.

Table B-7. Select Organ Weights in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]

Males: ADD [HED] in mg/kg-d				
Endpoint	**0 [0]**	**125 [18.3]**	**250 [36.6]**	**500 [73.7]**
Number evaluated (*n*)	19[b]	20	20	20
Necropsy body weight (g)	33.6 ± 3.22[c,d]	34.1 ± 1.86 (+1%)	34.5 ± 2.13 (+3%)	34.8 ± 2.09 (+4%)
Absolute liver (g)	1.689 ± 0.223	1.838 ± 0.146 (+9%)	2.028 ± 0.242 (+20%)**	2.288 ± 0.219 (+35%)**
Relative liver (% body weight)	5.020 ±0.413	5.389 ± 0.313 (+7%)*	5.865 ± 0.442 (+17%)**	6.588 ± 0.601 (+31%)**
Absolute kidney (g)	0.608 ± 0.108	0.628 ± 0.052 (+3%)	0.658 ± 0.072 (+8%)	0.681 ±0.077 (+12%)*
Relative kidney (% body weight)	1.807 ± 0.253	1.843 ±0.160 (+2%)	1.908 ± 0.173 (+6%)	1.958 ±0.180 (+8%)*
Absolute spleen (g)	0.084 ± 0.029	0.083 ± 0.018 (−1%)	0.110 ± 0.025 (+31%)*	0.173 ± 0.044 (+106%)**
Relative spleen (% body weight)	0.249 ± 0.075	0.244 ± 0.049 (−2%)	0.318 ± 0.074 (+28%)*	0.497 ± 0.13 (+99%)**
Absolute brain (g)	0.501 ± 0.027	0.498 ± 0.024 (−1%)	0.512 ± 0.036 (+2%)	0.505 ± 0.024 (+1%)
Relative brain (% body weight)	1.501 ± 0.130	1.466 ± 0.117 (−2%)	1.487 ± 0.100 (−1%)	1.457 ± 0.10 (−3%)
	Females: ADD [HED] in mg/kg-d			
	0 [0]	**125 [17.4]**	**250 [34.7]**	**500 [70.1]**
Number evaluated (*n*)	19[b]	19[b]	20	19[b]
Necropsy body weight (g)	27.3 ± 1.86	27.4 ± 1.93 (+0%)	27.9 ± 2.09 (+2%)	29.4 ± 2.00 (+8%)**
Absolute liver (g)	1.371 ± 0.167	1.490 ± 0.170 (+9%)	1.708 ± 0.223 (+25%)**	1.986 ± 0.195 (+45%)**
Relative liver (% body weight)	5.025 ± 0.439	5.432 ± 0.450 (+8%)*	6.101 ± 0.465 (+21%)**	6.759 ± 0.374 (+35%)**
Absolute kidney (g)	0.414 ± 0.032	0.418 ± 0.048 (+1%)	0.387 ± 0.074 (−7%)	0.433 ± 0.039 (+5%)
Relative kidney (% body weight)[e]	1.519 ± 0.097	1.524 ± 0.134 (+0%)	1.388 ± 0.257 (−9%)[f]	1.474 ± 0.101 (−3%)
Absolute spleen (g)	0.091 ± 0.028	0.100 ± 0.018 (+10%)	0.123 ± 0.027 (+35%)**	0.181 ± 0.052 (+99%)**
Relative spleen (% body weight)	0.333 ± 0.098	0.365 ± 0.068 (+10%)	0.443 ± 0.103 (+33%)**	0.612 ± 0.163 (+84%)**

Table B-7. Select Organ Weights in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]				
Absolute brain	0.507 ± 0.040	0.507 ± 0.042 (+0%)	0.490 ± 0.028 (−3%)	0.498 ± 0.034 (−2%)
Relative brain (% body weight)	1.865 ± 0.157	1.855 ± 0.141 (−1%)	1.764 ± 0.157 (−5%)	1.700 ± 0.125 (−9%)**

[a]TRL (1989).
[b]An animal died prior to terminal sacrifice (death was attributed by the study authors to gavage error).
[c]Data are means ± SD.
[d]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[e]Variance data were not legible in the study report. Variance data were calculated for this review from individual kidney weight data.
[f]Includes data for one animal (141) with kidney weight ~3 times lower than the others in this group (0.13 g, compared to a range of 0.35−0.49 g for other animals).
*Significantly different from control by Dunnett's test ($p < 0.05$), as reported by the study authors.
**Significantly different from control by Dunnett's test ($p < 0.01$), as reported by the study authors.

ADD = adjusted daily dose; HED = human equivalent dose; SD = standard deviation.

Table B-8. Select Histopathological Effects in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]				
Males: ADD [HED] in mg/kg-d				
Effect	**0 [0]**	**125 [18.3]**	**250 [36.6]**	**500 [73.7]**
Liver				
Pigment; Kupffer cells	0/20 (0%)[b]	0/20 (0%)	0/20 (0%)	12/20 (60%)*
Cytomegaly; centrilobular	0/20 (0%)	0/20 (0%)	3/20 (15%)	14/20 (70%)*
Cytologic alteration; centrilobular	0/20 (0%)	0/20 (0%)	1/20 (5%)	7/20 (35%)*
Spleen; hemosiderosis				
Minimal	0/20 (0%)	1/20 (5%)	7/20 (35%)*	3/20 (15%)
Mild	0/20 (0%)	0/20 (0%)	7/20 (35%)*	12/20 (60%)*
Moderate	0/20 (0%)	0/20 (0%)	0/20 (0%)	5/20 (25%)*
Total	0/20 (0%)	1/20 (5%)	14/20 (70%)*	20/20 (100%)*
Spleen; hematopoietic cell proliferation				
Minimal	0/20 (0%)	0/20 (0%)	7/20 (35%)*	2/20 (10%)
Mild	0/20 (0%)	0/20 (0%)	1/20 (5%)	14/20 (70%)*
Moderate	0/20 (0%)	0/20 (0%)	0/20 (0%)	2/20 (10%)
Total	0/20 (0%)	0/20 (0%)	8/20 (40%)*	18/20 (90%)*
Testes				
Degeneration	0/20 (0%)	0/20 (0%)	0/20 (0%)	5/20 (25%)*
Hypospermia	0/20 (0%)	0/20 (0%)	0/20 (0%)	2/20 (10%)

Table B-8. Select Histopathological Effects in Crl:CD-1 Mice Administered Fluorene via Gavage for 13 Weeks[a]

Females: ADD [HED] in mg/kg-d				
	0 [0]	**125 [17.4]**	**250 [34.7]**	**500 [70.1][c]**
Liver				
Pigment; Kupffer cells	0/20 (0%)	0/20 (0%)	0/20 (0%)	4/20 (20%)
Cytomegaly; centrilobular	0/20 (0%)	0/20 (0%)	0/20 (0%)	1/20 (5%)
Cytologic alteration; centrilobular	NR	NR	NR	NR
Spleen; hemosiderosis				
Minimal	0/20 (0%)	7/20 (35%)*	10/20 (50%)*	3/20 (15%)
Mild	0/20 (0%)	3/20 (15%)	6/20 (30%)*	13/20 (65%)*
Moderate	0/20 (0%)	0/20 (0%)	0/20 (0%)	4/20 (20%)
Total	0/20 (0%)	10/20 (50%)*	16/20 (80%)*	20/20 (100%)*
Spleen; hematopoietic cell proliferation				
Minimal	1/20 (5%)	3/20 (15%)	8/20 (40%)*	5/20 (25%)
Mild	0/20 (0%)	0/20 (0%)	3/20 (15%)	13/20 (65%)*
Moderate	0/20 (0%)	0/20 (0%)	0/20 (0%)	2/20 (10%)
Total	1/20 (5%)	3/20 (15%)	11/20 (55%)*	20/20 (100%)*

[a]TRL (1989).
[b]Number affected/number examined (% incidence). Includes animals that died prior to terminal sacrifice.
[c]Two 500 mg/kg-day females (194 and 195) died during week 1 and were replaced with animals from the satellite group (199S and 200S); 199S and 200S were evaluated for histopathological effects.
*Statistically significant from control ($p < 0.05$) based on one-tailed Fisher's exact test performed for this review.

ADD = adjusted daily dose; HED = human equivalent dose; NR = not reported.

Table B-9. Measured Concentrations of Fluorene in a Study of Male Wistar Han Rats Exposed Nose-Only to Fluorene for 14 Days[a]

	Target concentration in mg/m^3 [HEC]			
Endpoint	**0 [0] (freely moving)**	**0 [0] (restrained)**	**0.01 [0.0025]**	**1 [0.25]**
Measured concentration (mg/m^3)				
Day 1	ND	ND	0.0097 ± 0.0004 (−3%)[b,c,d]	1.069 ± 0.0170 (+7%)*
Day 4	ND	ND	0.0097 ± 0.0002 (−3%)	0.9810 ± 0.136 (−2%)*

[a]Peiffer et al. (2013).
[b]Data are means ± SEM.
[c]Values provided in the study report as ppb were converted to mg/m^3 using the following equation: exposure in mg/m^3 = exposure in ppm × MW of fluorene ÷ 24.45, using a MW of fluorene of 166.22 g/mol (U.S. EPA, 2021b).
[d]Value in parentheses is % change relative to target concentration = ([measured concentration − target concentration] ÷ target concentration) × 100.
*Significantly different from the target concentration at ($p < 0.01$) by Dunnett t-test, as reported by the study authors.

HEC = human equivalent concentration; MW = molecular weight; ND = not detected; SEM = standard error of the mean.

Table B-10. Restraint Effects in Control Male Wistar Han Rats Exposed to Air for 14 Days[a]

	Target concentration in mg/m^3 [HEC]	
Endpoint	**0 [0] (freely moving)**	**0 [0] (restrained)**
Number evaluated (*n*)	12	12
Body weight (g)		
Day before habituation	243.22 ± 2.01[b,c]	246.89 ± 2.48 (+2%)
Day prior to initiation of exposure	282.56 ± 3.45	270.61 ± 2.95 (−4%)*
After 7 days exposure	303.00 ± 4.56	288.56 ± 4.10 (−5%)*
After 14 days exposure	317.83 ± 5.41	299.00 ± 4.97 (−6%)*
Open-field test		
Total number of crossed cases	117.8 ± 10.5	149.2 ± 8.1 (+27%)*
Y-maze		
Total arm entries	25.3 ± 1.1	32.6 ± 1.6 (+29%)**

[a]Peiffer et al. (2013).
[b]Data are means ± SEM.
[c]Value in parentheses is % change relative to freely-moving control = ([restrained control mean − freely-moving control mean] ÷ freely-moving control mean) × 100.
*Significantly different from control at ($p < 0.05$) by Dunnett t-test, as reported by the study authors.
**Significantly different from control at ($p < 0.01$) by Dunnett t-test, as reported by the study authors.

HEC = human equivalent concentration; SEM = standard error of the mean.

Table B-11. Behavioral Effects in Male Wistar Han Rats Exposed Nose-Only to Fluorene for 14 Days[a]

Target concentration in mg/m³ [HEC]			
Endpoint	**0 [0] (restrained)**	**0.01 [0.0025]**	**1 [0.25]**
Number evaluated (*n*)	12	12	12
Open-field test			
Number of crossed squares; central area	4.60[b,c]	8.60 (+87%)**	8.20 (+78%)*
Time; central area (s)	12.5	21.1 (+69%)*	11.4 (−9%)
Total number of crossed squares	149.5	159.6 (+7%)	163.3 (+9%)
Elevated-plus maze			
Central area time (s)	63.8 ± 6.3[d]	76.8 ± 5.4 (+20%)*	79.5 ± 4.6 (+25%)*
Open arm time (s)	87.5 ± 9.7	75.4 ± 12.7 (−14%)	71.7 ± 9.9 (−18%)
Closed arm time (s)	148.7 ± 11.2	147.8 ± 14.8 (−1%)	148.8 ± 10.7 (+0%)
Head dipping in open arms (%)	62.3 ± 5.7[e]	54.7 ± 7.4 (−8%)	40.0 ± 7.1 (−22%)[f]
Total head dipping	7.7 ± 0.8	8.3 ± 0.9 (+8%)	8.2 ± 1.2 (+6%)

[a]Peiffer et al. (2013).
[b]Data are means based on graphically reported data extracted using the MATLAB tool, GRABIT; variance values were not extracted.
[c]Value in parentheses is % change relative to control = ([treatment mean − control mean] ÷ control mean) × 100.
[d]Data are means ± SEM.
[e]Value in parentheses is % change relative to control = control mean − treatment mean (for data reported as %).
[f]$p = 0.08$ (marginal statistical significance) based on Dunnett t-test, as reported by the study authors.
*Significantly different from control at ($p < 0.05$) by Dunnett t-test, as reported by the study authors.
**Significantly different from control at ($p < 0.01$) by Dunnett t-test, as reported by the study authors.

HEC = human equivalent concentration; SEM = standard error of the mean.

APPENDIX C. REFERENCES

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