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# Provisional Peer Reviewed Toxicity Values for

**Pyrene**  
(CASRN 129-00-0)

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## Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose

PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

## **PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR PYRENE (CASRN 129-00-0)**

### **Background**

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).
2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.
3. Other (peer-reviewed) toxicity values, including:
  - ▶ Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
  - ▶ California Environmental Protection Agency (CalEPA) values, and
  - ▶ EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

### **Disclaimers**

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

### **Questions Regarding PPRTVs**

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

## **INTRODUCTION**

IRIS (U.S. EPA, 1997a) provides a chronic RfD of 3E-2 mg/kg-day developed from a NOAEL of 75 mg/kg-day with a combined uncertainty factor of 3000 (10 each for intra- and interspecies variability, 10 for the use of a subchronic study for chronic RfD derivation, and an additional 3 to account for the lack of both toxicity studies in a second species and developmental/reproductive studies) using a 13 week gavage study in mice, conducted by Toxicity Research Laboratories, Muskegon, MI (U.S. EPA, 1989) for the Office of Solid Waste, Washington, DC. The critical effects were renal tubular pathology and decreased kidney weights. IRIS (U.S. EPA, 2007) did not develop an RfC. IRIS (U.S. EPA, 2007) provided a classification of D, not classifiable as to human carcinogenicity based on no human data and inadequate data from animal experiments. A subchronic RfD is currently listed on HEAST of 3E-1 mg/kg-day which will be removed when this PPRTV is activated (U.S. EPA, 1997b). It was based on the same study as this PPRTV.

A cancer classification for pyrene of Group D is listed in the Drinking water Standard and Health Advisory lists (U.S. EPA, 2000) based on an assessment of pyrene from the Drinking Water Criteria Document for polycyclic aromatic hydrocarbons (U.S. EPA, 1990). The CARA lists (U.S. EPA, 1991, 1994) report a Health Effects Assessment (U.S. EPA 1984) and a Health and Environmental Effects Profile (HEEP) U.S. EPA 1987) for pyrene. ATSDR (2001) has not published a toxicological profile for pyrene, but it is included in the profile for polycyclic aromatic hydrocarbons (ATSDR, 1995). IARC has assigned pyrene to Group 3, not classifiable as to its carcinogenicity to humans, based on no human data and limited animal data (IARC, 1983, 1987). A multimedia document for polycyclic aromatic hydrocarbons (U.S. EPA, 1992) and the NTP status reports (NTP, 2001) were also searched to identify relevant data. Literature searches for all exposure routes and effects were conducted from 1989 to December 2000 and updated to 2007. The databases searched were: TOXLINE, TSCATS, CANCERLIT,

MEDLINE, GENETOX, HSDB, EMIC/EMIC/EMICBACK, DART/ETICBACK, CCRIS AND RTECS.

This document has passed the STSC quality review and peer review evaluation indicating that the quality is consistent with the SOPs and standards of the STSC and is suitable for use by registered users of the PPRTV system.

## **REVIEW OF THE PERTINENT LITERATURE**

### **Human Studies**

No human studies were located regarding exposure of humans to pyrene.

### **Animal Studies**

A U.S. EPA (1989) study conducted by Toxicity Research Laboratories, Muskegon MI for the Office of Solid Waste, Washington DC was the basis of IRIS's chronic RfD of  $3E-2$  mg/kg-day. Male and female CD-1 mice (20/sex/group) were gavaged with 0, 75, 125, or 250 mg/kg/day pyrene in corn oil for 13 weeks. The toxicological parameters examined in this study included body weight changes, food consumption, mortality, clinical pathological evaluations of major organs and tissues, and hematology and serum chemistry. Nephropathy, characterized by the presence of multiple foci of renal tubular regeneration, often accompanied by interstitial lymphocytic infiltrates and/or foci of interstitial fibrosis, was present in 4, 1, 1, and 9 male mice in the control, low-, medium-, and high-dose groups, respectively. Similar lesions were seen in 2, 3, 7, and 10 female mice in the 0, 75, 125, and 250 mg/kg treatment groups. The kidney lesions were described as minimal or mild in all dose groups. Relative and absolute kidney weights were reduced in the two higher dosage groups. Based on the results of this study, the low dose (75 mg/kg/day) was considered the NOAEL and 125 mg/kg/day the LOAEL for nephropathy and decreased kidney weights. The IRIS RfD of  $3E-2$  mg/kg-day was calculated using a composite uncertainty factor of 3000, including 10 each for intra- and interspecies variability, and an additional 3 to account for the lack of both toxicity studies in a second species and developmental/reproductive studies and 10 for extrapolation from subchronic to chronic.

White and White (1939) fed six male rats (unspecified strain) a diet containing 2000 mg pyrene/kg for 40 days. The average reported food intake for two animals was 6.1 g/day, and the average body weight for these two animals was 94.3 g. A decrease in body weight gain was observed in two animals. The authors stated that this body weight gain was representative of the whole group; although there was no change in food intake. White and White (1939) also observed enlarged livers and increased hepatic lipid content in animals treated with pyrene, benzo[a]pyrene or methylcholanthrene in the diet; however, incidence data were not reported and it is unclear whether this effect occurred in the pyrene treated rats. Interpretation of this study is further complicated by the lack of experimental controls and statistical analysis, small sample size, and incomplete reporting of histopathology results.

No other useful studies are available that examine only pyrene exposure

## Other studies

Pyrene has been assayed for genotoxicity in a number of tests with both positive and negative results. These have been extensively reviewed by EPA (U.S. EPA, 1984, 1987, 2000, 2001) and only those studies published since the most recent EPA review was performed are included in the following text.

*In vitro* genotoxicity tests of pyrene in prokaryotic systems have produced mixed results. The consensus conclusion on the WHO international collaborative study (which involved 20 bacterial test sets) was that protocol or evaluation criteria were critical factors in individual test verdicts (WHO, 1990). Pyrene has been shown to bind to DNA (Chen, 1983) and to form DNA adducts (Segerback and Vodicka, 1993), but was not mutagenic in DNA damage assays in *Escherichia coli* and *Bacillus subtilis* (Hellmer and Bolcsfold, 1992; Kranendonk et al., 1994, 1996; Mersch-Sundermann et al., 1992, 1993; Rossman et al., 1991). Both positive (Johnson, 1992) and negative (Rexroat et al., 1995; Rusina et al., 1992; Van der Lelie et al., 1997) results have been reported in bacterial gene mutation tests. Pyrene induced increased incidence of mitotic gene conversion but not other genetic endpoints in yeast (deSerres et al., 1981).

Most *in vitro* tests in mammalian cells have given negative results. Pyrene gave mixed results in tests of unscheduled DNA synthesis (Heil and Reifferscheid, 1992; Selden et al., 1994) and was mostly negative in tests for sister chromatid exchange and negative for chromosome aberrations (Darroudi and Natarajan, 1993; Natarajan and Darroudi, 1991). Pyrene was mutagenic in the L5178Y mouse lymphoma gene mutation assay when metabolically activated (Oberly et al., 1993), but was not mutagenic in metabolically competent human lymphoblastoid cells (Busby et al., 1994; Durant et al., 1996) and did not induce micronucleus formation in a variety of mammalian cell types (Crofton-Sleigh et al., 1993; Fritzenschaf et al., 1993; Muller-Tegethoff et al., 1995; Natarajan and Darroudi, 1991; Neslany and Marzin, 1999). Results of mammalian cell transformation assays have also been negative (U.S. EPA, 2000).

*In vivo* genotoxicity tests of pyrene have also produced mostly negative results. Pyrene produced no increase or only a slight increase in sex-linked recessive lethals in *Drosophila* and was negative in the *Drosophila* eye mosaic assay (Fujikawa et al., 1993; Vogel and Nivard, 1993). Application of pyrene to the skin of hairless mice produced no increase in micronucleus induction in keratinocytes (He and Baker, 1991). Pyrene was positive in the newt micronucleus test (Fernandez et al., 1989).

## DERIVATION OF A PROVISIONAL SUBCHRONIC OR CHRONIC RfD FOR PYRENE

A U.S. EPA (1989) study conducted by Toxicity Research Laboratories, Muskegon MI for the Office of Solid Waste, Washington DC was utilized by IRIS for development of a chronic RfD. This study was selected for development of a provisional subchronic RfD. Based on the results of this study, the low dose (75 mg/kg/day) was considered the NOAEL and 125 mg/kg/day the LOAEL for nephropathy and decreased kidney weights.

A composite uncertainty factor of 300 was applied to the NOAEL of 75 mg/kg-day; 10 each for intra- and interspecies variability, and an additional 3 to account for the lack of both toxicity studies in a second species and developmental/reproductive studies providing a **subchronic RfD of 0.25 mg/kg-day or 3E-1 mg/kg-day**.

**NOAEL/ Uncertainty Factors = 75/300 = 0.25 or 3E-1 mg/kg-day**

Confidence in the principal study is medium, as it was a well-designed experiment that examined a variety of toxicological endpoints and identified both a NOAEL and LOAEL for the critical effect. Confidence in the database is low, due to the lack of supporting subchronic, chronic, and developmental/reproductive studies. Accordingly, confidence in the provisional subchronic RfD is low.

### **DERIVATION OF A PROVISIONAL SUBCHRONIC OR CHRONIC RfC FOR PYRENE**

No provisional RfC is developed due to lack of usable information.

### **PROVISIONAL CARCINOGENICITY ASSESSMENT FOR PYRENE**

IRIS (U.S. EPA, 2007) provides no quantitative assessments (OSF or IUR) for pyrene and classifies it as classification of D, not classifiable as to human carcinogenicity based on no human data and inadequate data from animal experiments. Based on the U.S. EPA (2005) Cancer Guidelines, pyrene can be classified as “not likely to be a human carcinogen”.

No data is currently available and suitable for developing cancer values.

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