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Provisional Peer Reviewed Toxicity Values for

Perylene
(CASRN 198-55-0)

Superfund Health Risk Technical Support Center
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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 PERYLENE (CASRN 198-55-0)

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

Perylene (CASRN 198-55-0; molecular weight = 252.3) is a polycyclic aromatic hydrocarbon (PAH) with 5 fused, 6-membered rings. Synonyms for perylene include dibenz[de,kl]anthracene and peri-dinaphthalene (IARC, 1998). Isomers of perylene include benzo[a]pyrene and benzo[e]pyrene. Perylene, like other polycyclic aromatic hydrocarbons (PAH), is formed during the combustion or pyrolysis of carbon-containing materials including coal and mineral oils (IARC, 1983; ATSDR, 1995). Demonstration of PAH formation in high temperatures include observations that concentrations of PAHs in lubricating oils increase with continued use at high temperatures (e.g., Apostoli et al., 1993).

This paper evaluates available information on carcinogenic and non-carcinogenic health effects in humans and animals exposed orally and by inhalation to perylene. Classification of perylene in the U.S. EPA (2005) cancer weight-of-evidence scheme is considered, as well as potential derivation of a cancer oral slope factor, a cancer inhalation unit risk, subchronic and chronic oral RfD, and subchronic and chronic inhalation RfC.

Neither a reference dose (RfD) nor a reference concentration (RfC) were available for perylene in the Integrated Risk Information System (IRIS) database (U.S. EPA, 2007) or the Health Effects Assessment Summary Tables (HEAST; U.S. EPA, 1997). There was no Agency for Toxic Substances and Disease Registry (ATSDR) Toxicological Profile on perylene (ATSDR, 2007). Health assessments for perylene were not available from other major sources, including CalEPA (2007), the National Toxicology Program (NTP, 2007), or the World Health Organization (WHO, 2007). Occupational exposure limits were not available from the American

Conference of Industrial Hygienists (ACGIH) (2007), National Institute for Occupational Safety and Health (NIOSH) (2005) or Occupational Safety and Health Administration (OSHA) (2007). Perylene was not listed on HEAST (U.S. EPA, 1997), the Chemical Assessments and Related Activities (CARA) lists (U.S. EPA, 1991, 1994) or the Drinking Water Health Advisories list (U.S. EPA, 2006). Perylene had not been studied by NTP (2007), and was not among the 17 PAHs discussed in the ATSDR (1995) Toxicological Profile for Polycyclic Aromatic Hydrocarbons or the 15 PAHs discussed in the U.S. EPA (1990) Drinking Water Criteria Document for Polycyclic Aromatic Hydrocarbons. IARC (1998), however, prepared a review of the carcinogenicity and mutagenicity of perylene.

Searches of TOXLINE were conducted (1983-1991 in May, 1991; 1991-September 1995 in August, 1995; 1981-1991 and after September, 1995 in January 1996 and June 2007) to identify reports of studies with health effects data for perylene. A CASRN and synonym strategy was employed using oral, inhalation, and cancer terms in the searches. Searches of CANCERLINE (1991- 1995 in August, 1995; 1981-1995 in January, 1996; and 1995-2007 in June 2007) also were conducted, as were searches of the RTECS, TSCATS, MEDLINE, CCRIS, DART, GENETOX, EMIC, EMICBACK and ETICBACK databases.

REVIEW OF PERTINENT DATA

Human Studies

Studies directly examining the toxicity or carcinogenicity of perylene in humans were not located. Perylene has been present in the environment as a component of complex PAH-containing combustion product mixtures, several of which are known or suspected to be carcinogenic in humans (e.g., coal tars, soot, and tobacco smoke and products; see IARC, 1983, 1998). However, results from studies of these mixtures were inadequate to evaluate the toxicity or carcinogenicity of perylene or other individual PAH components.

Animal Studies

No studies were located regarding cancer or noncancer effects in animals after oral or inhalation exposure. Available cancer bioassays in animals were limited to mouse studies with dermal exposure or i.p. injection.

Data from several tumor assays following dermal exposure are summarized in Table 1. In a skin tumor initiation assay, Van Duuren et al. (1970) applied single doses of 800 μg perylene (purified by recrystallization) in 200 μL benzene to the clipped dorsal skin of a group of 20 female ICR/Ha Swiss mice, six- to eight-weeks old. No skin tumors were found during a 58-60 week observation period. Another group of 20 mice received single dermal doses of perylene at the same level. These were followed, beginning 2 weeks later, by three times per week application of 2.5 μg 12-O-tetradecanoylphorbol-13-acetate (TPA) in 0.1 mL acetone during the 58-60 week observation period. Skin papillomas were found in 3/20 mice in the perylene/TPA

TABLE 1: Tumor data from dermal application of perylene

Species and Study Type	Exposure	Critical Effects	Comments	Reference
Mouse Dermal Carcinogenicity	Twice weekly dermal application of 60 µL for up to 82 weeks	No significant increase in skin tumors	Examinations apparently limited to application site	Horton and Christian, 1974
Mouse Dermal Carcinogenicity	Single 800 µg dermal dose followed by 58-60 weeks of observation	No significant increase in skin tumors	Examinations apparently limited to application site	Van Duuren et al., 1970
Mouse Skin Tumor Initiation	Single 800 µg dermal dose followed by thrice weekly application of TPA for 58-60 weeks	No significant increase in skin tumors	Examinations apparently limited to application site	Van Duuren et al. 1970
Mouse Skin Tumor Initiation	Single 1 mg dermal dose followed by thrice weekly application of TPA for 25 weeks	No significant increase in skin tumors or tumors at other sites	Skin tumors were evaluated histologically and animals were examined for visible tumors at other sites	El-Bayoumy et al., 1982
Mouse Dermal Carcinogenicity[d]	Thrice weekly dermal application of 1% perylene for 1 year	No significant increase in skin tumors	Study poorly reported as an abstract	Anderson and Anderson 1987
Mouse Skin Tumor Promotion[d]	Single 300 µg dermal dose of benzo(a)pyrene followed by thrice weekly dermal application of 1% perylene for 1 year	No significant increase in skin tumors compared to treatment without benzo(a)pyrene initiation.	Study poorly reported as an abstract	Anderson and Anderson 1987
Mouse (Strain A) Lung Tumor Initiation[d]	Thrice weekly i.p. injection of 200, 500 or 1000 mg/kg perylene for 8 weeks followed by 16 weeks of observation	No significant increase in lung adenomas in Strain A mouse model system for detection of tumor initiation.	Study poorly reported as an abstract	Anderson and Anderson 1987

group compared with 0/20 in an acetone control group and 1/20 in a TPA control group. The report did not mention a benzene control group. Differences in tumor incidence between the perylene group and either of the control groups were not statistically significant, using the Fisher Exact test conducted for this document, and p=0.05 as the criteria of significance.

Horton and Christian (1974) applied 60 µL of a 0.15% solution of perylene (purified by recrystallization) in decalin twice weekly for up to 82 weeks to the dorsal skin of 20 male C3H mice, beginning at two months of age. At 52 weeks, 16/20 of the mice had survived without showing skin tumors. Details were not provided regarding the 4 mice that died during the first 52 weeks. During the following 30 weeks, no skin tumors developed in the 16 mice that survived 52 weeks. A decalin-only control group was not included, but in a group of 20 mice treated with a 50:50 mixture of dodecane and decalin twice weekly for up to 82 weeks, 2/13 mice that survived at least 52 weeks developed skin papillomas, although no carcinomas were found.

El-Bayoumy et al. (1982) compared the mouse skin tumor initiation activities of several PAHs, including perylene and benzo[a]pyrene. Test compounds (> 99% pure by HPLC analysis) were dissolved in acetone and applied in 10 doses, every other day, to the shaved backs of groups of 20 Crl/CD-1(ICR)BR female mice. The total initiation dose was 1 mg/mouse for perylene and 0.05 mg/mouse for benzo[a]pyrene. Ten days after initiation, 2.5 µg tetradecanoylphorbol acetate (TPA) in 0.1 mL acetone was applied three times weekly for 25 weeks, after which the animals were autopsied. At autopsy, skin tumors were examined histologically and animals were examined for visible tumors at other sites. One non-skin tumor was found in the vehicle control group (acetone initiation and TPA promotion). In the group given initiating doses of 1 mg perylene/mouse, 5% (1/20) had skin tumors with an average 0.1 skin tumors per mouse. Skin tumors were reported to be predominately squamous cell papillomas. This tumorigenic response was identical to that in the vehicle control group. In the group initiated with benzo[a]pyrene (0.05 mg/mouse), 90% (18/20) had skin tumors with an average 7.1 skin tumors/mouse. These results suggest that the perylene might not be tumorigenic in mouse skin.

Anderson and Anderson (1987) applied 1% perylene to mouse skin tree times per week for one year. No increase in the rate of skin tumors was reported in this abstract. Likewise, among mice similarly treated with perylene following a single 300 µg dermal dose of benzo(a)pyrene they reported no significant increase in skin tumors compared to treatment without benzo(a)pyrene initiation. Finally, among mice injected (i.p.) three times weekly for eight weeks with 200-1000 mg/kg perylene, and observed for 16 additional weeks, they reported no increase in lung adenomas.

In summary, no statistically significant tumorigenic responses to perylene were found in two mouse-skin tumor-initiation assays (Van Duuren et al., 1970; El-Bayoumy et al., 1982) or in an 82-week mouse skin complete carcinogenicity assay (Horton and Christian, 1974). Comparison of the skin tumor initiation activity of perylene with that of its isomer, benzo[a]pyrene, suggested that if perylene is tumorigenic in mouse skin, its potency is much less than that of benzo[a]pyrene (El-Bayoumy et al., 1982). Animal cancer bioassays in other animal species or examining routes of exposure other than dermal or intraperitoneal were not located.

Other Studies

The animal data discussed in the previous section and the supporting data discussed in this section suggest that, if perylene is carcinogenic or genotoxic, its potency is likely to be much less than that of its isomer, benzo[a]pyrene, one of the most potent carcinogenic PAHs studied to date.

In the presence of rat liver metabolic activation systems ("S9") from rats pretreated with the polychlorinated biphenyl, Aroclor 1254, perylene produced mutagenic effects in numerous *Salmonella typhimurium* reverse mutation assays using a 2-fold increase in reversion rate as the criteria of mutagenicity. The results from the various laboratories, however, did not consistently identify the same strains as being responsive to perylene (Anderson and Styles, 1978; Kaden et al., 1979; LaVoie et al., 1979; Florin et al., 1980; Ho et al., 1981; DeFlora et al., 1984; Sakai et al., 1985; Carver et al., 1985). One laboratory, Salamone et al. (1979), found that, in the presence of S9 activation, perylene concentrations up to 1000 μg/plate did not increase the rate of reverse mutations in any of 5 tested strains (TA98, TA100, TA1535, TA1537, TA 1538), by the two-fold increase criteria.

Sakai et al. (1985) reported that perylene at concentrations up to 50 μg/plate increased reverse mutations at the histidine locus only in the presence of S9 activation, in strain TA97 but not in strains TA98 or TA100. In contrast, LaVoie et al. (1979) and Ho et al. (1981) reported that perylene was mutagenic at the same locus at 10 μg/plate in strain TA100 and at 5 μg/plate in strain TA98, respectively, both in the presence of S9 activation only. Anderson and Styles (1978) found that 100 μg perylene/plate, in the presence of S9 activation, increased reverse mutations at the histidine locus by 10-fold, compared with negative control conditions, in strain TA1535 and 4-fold at 4 μg/plate, in strain TA100. However, they found no mutagenic activity in strains TA1538 or TA98 at concentrations up to 2500 μg/plate. DeFlora et al. (1984) found that perylene in the presence of S9 activation increased reverse mutations compared with negative control conditions in strains TA1538, TA98, TA1537, but not in strains TA97 or TA1535. Florin et al. (1980) found that perylene in the presence of S9 activation significantly increased reverse mutations in strain TA98, but not in strain TA100. Carver et al. (1985, 1986) found perylene-induced mutagenic activity at 50 μg/plate with S9, in strains TA98 and TA100, and found that the degree of activity increased with increasing concentrations of S9.

Comparison of the mutagenic activities of perylene and benzo[a]pyrene in *Salmonella typhimurium* reverse mutation assays suggested that the mutagenic potency of perylene might be less than that of benzo[a]pyrene (Florin et al., 1980; DeFlora et al., 1984; Carver et al., 1985). Florin et al. (1980) reported that an optimal mutagenic dose of benzo[a]pyrene, 0.003 μmol/plate, produced 235 revertants/plate in strain TA98, whereas an optimal dose of perylene, 0.025 μmol/plate, produced 91 revertants/plate in the same strain. DeFlora et al. (1984) reported that the mutagenic potency of benzo[a]pyrene, measured as the number of revertants in the most sensitive strain divided by the corresponding dose of compound (nmole/plate), was approximately 9-fold greater than that of perylene (185 versus 21 revertants/nmole). Carver et al. (1985) found that 1.0 μg benzo[a]pyrene/plate, in the presence of 15 μL S9, produced reversion rates similar to those produced by 50 μg perylene/plate in the presence of 240 μL S9.

In contrast to the *S. typhimurium* reverse mutation results, Penman et al. (1980) reported that a 40 micromolar (μmol) concentration of perylene in the presence of S9 produced forward mutation rates for 8-azaguanine resistance in *S. typhimurium* strain TM677 that were similar to those produced by 40 μmol benzo[a]pyrene under similar conditions (approximately 30 versus 43 "induced mutant fraction x 10^5" for perylene and benzo[a]pyrene, respectively).

Hera and Pueyo (1988) found that at concentrations up to 400 nmol perylene/plate, in the presence of S9, did not significantly increase the reversion rate of histidine-locus mutations in *S. typhimurium* strain TA97, but significantly increased the frequency of L-arabinose-resistant mutants in strain BA9 in the presence of a high concentration of S9.

Kaden et al. (1979) reported that 1 nmol perylene/mL was mutagenic in the presence of metabolic activation at the $8AG^s/8AG^r$ locus in *S. typhimurium* strain TM677.

Mersch-Sundermann et al. (1992) found no evidence for perylene genotoxicity in *Escherichia coli* PQ37 using the SOS Chromotest for DNA damage, in the presence or absence of S9 activation. This assay indirectly measured DNA damage by measuring induction of the SOS-DNA repair system. In contrast, benzo[a]pyrene, in the presence of S9 activation, markedly induced the SOS-DNA repair system in *E. coli* PQ37. von der Hude et al. (1988) reported similar results comparing perylene and benzo[a]pyrene in the same SOS chromotest with *E. coli* PQ37.

In *in vitro* assays, Popescu et al. (1977) found that incubation of Chinese hamster V79 cells for 24 hours in10 μg/mL perylene did not induce sister chromatid exchanges (SCE). However, chromosome aberrations were found in more cells treated with perylene than in control cells, but a statistical analysis was not conducted. Sirianni and Huang (1978) examined SCE frequencies in Chinese hamster V-79 cells that were contained in diffusion chambers implanted in the peritoneal cavities of mice; V-79 cells were examined for SCE frequencies 22 hours after intraperitoneal injection of a test compound. 25-150 μg Perylene/g mouse body weight) did not significantly increase SCE frequencies in the V-79 cells compared with V-79 cells implanted in mice without injection of a test compound. In contrast, injection of 25-150 μg benzo[a]pyrene/g mouse body weight, produced statistically significant, dose-related increases in SCE frequencies in V-79 cells.

Crespi and Thilly (1984) compared the abilities of perylene and benzo[a]pyrene to induce 6-thioguanine-resistant mutations in a human lymphoblast cell line, AHH-1. Incubation of the cells in benzo[a]pyrene concentrations $\geq$ 3 μmol for 24 hours significantly increased the mutant frequency compared with control conditions. In contrast, incubation of the cells in medium containing up to 20 μmol perylene for 48 hours did not produce statistically significant increases in the mutation frequency.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC ORAL RfD VALUES FOR PERYLENE

No studies were located regarding non-carcinogenic effects in humans or animals after oral exposure to perylene. Due to the lack of data, no RfDs were derived for perylene.

DERIVATION OF PROVISIONAL SUBCHRONIC AND CHRONIC INHALATION RfC VALUES FOR PERYLENE

No studies were located regarding non-carcinogenic effects in humans or animals after inhalation exposure to perylene. Due to the lack of data, no RfC was derived for perylene.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR PERYLENE

Weight-of-Evidence Classification for Perylene

No studies were located examining associations between cancer and exposure of humans to perylene. Perylene is a component of several complex mixtures containing PAHs, including tobacco smoke and soot, that are demonstrated human carcinogens. However, the available data did not determine what role, if any, perylene played in the carcinogenic responses to these mixtures. Thus, there were inadequate human data to assess the carcinogenicity of perylene.

Data examining the potential for perylene to produce cancer in animals were restricted to several mouse skin tumor assays that found no perylene-induced increases in incidence of skin or distant site tumors. U.S. EPA guidelines (2005) indicated that, in order to classify data from animal studies as providing no evidence of carcinogenicity, no increased incidence of neoplasms should be found in at least two-well designed and well-conducted animal studies of adequate power and dose in different species. Thus, the available animal data for perylene were not sufficient to classify them as providing no evidence of carcinogenicity. Alternatively, the animal data were classified as providing inadequate evidence. Additional well-conducted testing in other animal species with long-term exposure, preferably via oral and inhalation exposure, is necessary to provide reasonable assurance as to whether perylene may or may not be carcinogenic in animals or humans.

The genotoxicity of perylene was tested in several short-term genotoxicity assays in bacteria and in *in vitro* mammalian systems. Although perylene induced genotoxic effects in several of these test systems, comparisons of perylene genotoxic potency with that of its carcinogenic isomer, benzo[a]pyrene, generally found perylene to be a less potent genotoxic agent.

Following U.S. EPA (2005) guidelines for compounds with inadequate human data and inadequate animal data, perylene was classified as having inadequate information to assess carcinogenic potential.

Quantitative Estimates of Carcinogenic Risk for Perylene

Due to inadequate information to assess carcinogenic potential, a quantitative cancer risk estimate for neither an oral slope factor nor an inhalation unit risk could be derived for perylene.

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