MICHIGAN DEPARTMENT OF ENVIRONMENT, GREAT LAKES, AND ENERGY

INTEROFFICE COMMUNICATION

TO: File for Phenanthrene (CAS # 85-01-8)

FROM: Doreen Lehner, Toxics Unit, Air Quality Division

DATE: May 19, 2020

SUBJECT: Screening Level for Phenanthrene (CAS # 85-01-8)

The initial threshold screening level (ITSL) for phenanthrene (CAS # 85-01-8) is 0.1 µg/m^3 based on an annual averaging time. The ITSL for phenanthrene was established at the default value of 0.1 µg/m^3 (annual averaging time) on 9/15/1999 and was also reviewed 11/6/2013. An updated review was requested to see if any new toxicity data was available from which to derive an ITSL. No new data was found and the ITSL for phenanthrene remains at 0.1 µg/m^3 (annual averaging time).

Phenanthrene (CAS # 85-01-8) also known as tricyclo[8.4.0.0^{2,7}]tetradeca-1,3,5,7,9,11,13-heptaene is a polycyclic aromatic hydrocarbon composed of three fused benzene rings (see Figure 1). Phenanthrene is a colorless, crystalline solid that is nearly insoluble in water, but is soluble in organic solvents such as: toluene, carbon tetrachloride, ether, chloroform, acetic acid, and benzene. Phenanthrene is found in cigarette smoke. Phenanthrene is used in the manufacture of dyes, plastics, pesticides, explosives, drugs, bile acids, cholesterol, and steroids.

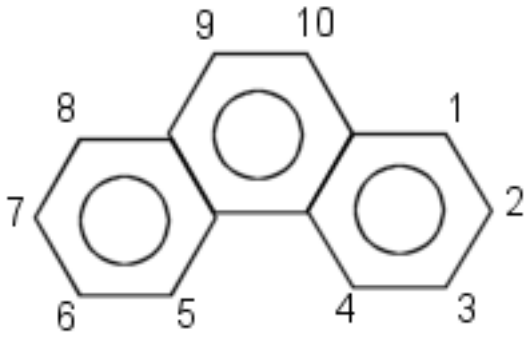


Figure 1. Structure of phenanthrene.

A thorough literature review was conducted to determine an initial threshold screening level (ITSL) for phenanthrene. The following references and databases were searched to derive the above screening level: United States Environmental Protection Agency (US EPA) Integrated Risk Information System (IRIS), National Institute for Occupational Safety and Health (NIOSH), American Conference of Governmental and Industrial Hygienists (ACGIH) Threshold Limit Values and Biological Exposure Indices (TLV/BEI) 2019 guide, National Toxicology Program (NTP) Study Database, International Agency for Research on Cancer (IARC), Scifinder

Chemical Abstract Service (CAS) Online (searched 5/6/2020), PubChem, PubMed, US EPA ChemView, US EPA Chemistry Dashboard, US EPA Provisional Peer Review Toxicity Values, and the Canadian Centre for Occupational Health and Safety (CCOHS) Registry of Toxic Effects of Chemical Substances (RTECS) Database.

RfC or RfD values were unavailable. There is no occupational exposure limit data available for this compound. There are no 7-day inhalation studies that would yield a LOAEL or NOAEL and no acute inhalation data where an LC_{50} can be derived. Based on Rule 232(1)(i) the ITSL is set at the default of 0.1 µg/m^3. According to Rule 232(2)(c), the averaging time is annual.

Based on the above data, the initial threshold screening level (ITSL) for phenanthrene (CAS # 85-01-8) is 0.1 µg/m^3 annual averaging time.

References:

Act 451 of 1994. Part 55, Air Pollution Control, of the Natural Resources and Environmental Protection Act, 1994 PA 451, as amended.

DL:lh

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

November 6, 2013

TO: File for Phenanthrene (CAS No. 85-01-8)

FROM: Michael Depa, Toxics Unit, Air Quality Division

SUBJECT: Screening Level

The ITSL for phenanthrene was established at the default value of 0.1 ug/m^3 (annual averaging time) on 9/15/99 after a thorough literature review did not reveal sufficient toxicological data to derive an ITSL (see attached 9/20/16 memo). As an update, a literature review (including EPA's IRIS and PPRTV databases, and a July 24, 2012 search of the Chemical Abstracts Service) was recently completed. This updated literature search did not produce studies adequate for development of a new screening level. There are not sufficient data to indicate that phenanthrene is carcinogenic by inhalation; skin painting studies indicate that phenanthrene is not carcinogenic (EPA, 2010). Structure activity relationships with other polycyclic aromatic hydrocarbons (PAHs) or a computational toxicology methodology may be useful in deriving a screening level in the future. However, these novel quantitative risk assessment techniques require specific metabolic and toxicokinetic information that is not readily available for phenanthrene. Furthermore, this type of risk assessment would require a significant amount of time and preparation. Therefore, the screening level will remain at the default screening level of 0.1 µg/m^3, with annual averaging time.

Reference

EPA, 2010. Development of a Relative Potency Factor (RPF) Approach for Polycyclic Aromatic Hydrocarbon (PAH) Mixtures: In Support of Summary Information on the Integrated Risk Information System (IRIS). February 2010. External Review Draft – Do Not Cite Or Quote. EPA/635/R-08/012A. 662 pages. Downloaded 9-5-2012

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

September 20, 1999

TO: File for Phenanthrene (CAS # 85-01-8)

FROM: Dan O'Brien

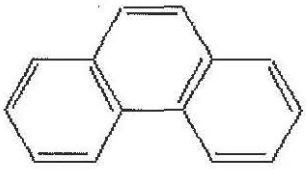
SUBJECT: Initial Threshold Screening Level (ITSL) for Phenanthrene

The initial threshold screening level for phenanthrene is 0.1 µg/m^3 based on an annual averaging time.

The following references or databases were searched to identify data to determine the ITSL: AQD chemical files, IRIS, HEAST, ACGIH TLV Booklet, NIOSH Pocket Guide to Chemical Hazards, RTECS, NTP Management Status Report, EPB Library, IARC Monographs, CAS On-line and NLM/Toxline (1967 – October 7, 1998), CESARS, Patty's Industrial Hygiene and Toxicology, Merck Index and Condensed Chemical Dictionary.

Phenanthrene (Ph) is a colorless, shining crystalline solid (Merck, 1983; Hawley, 1981). One of a group of polycyclic aromatic hydrocarbons (PAHs), it is an isomer of anthracene (120-12-7), and is a common component of coal tar and several types of crude petroleum (Cavender, 1994). It is used in dyestuffs and explosives; in biochemical research; and in the synthesis of drugs (Verschueren, 1983; Hawley, 1981). The chemical structure of the compound is illustrated in Figure 1.

Figure 1.



With respect to acute toxicity, RTECS (1996) cites a Russian oral LD_{50} (Anonymous, 1964) in mice of 700 mg/kg. However, this dose seems somewhat inconsistent with another RTECS citation of the same Russian study. That citation lists a lowest published toxic dose *via* the oral route in mice as 6370 mg/kg for a 13 week intermittent exposure. The only other acute studies found in our searches were also cited in RTECS, LD_{50}s of 700 mg/kg and 56 mg/kg in mice, *via* the intraperitoneal and intravenous routes, respectively.

ATSDR has published a massive Toxicological Profile for the PAHs as a group (1995). While there is no specific health risk evaluation concerning the inhalation of Ph *per se*, the work does an admirable job summarizing the available data for the chemical, and the rest of the PAHs. Because of the comprehensiveness of

this document, only selected topics of relevance to the derivation of a screening level will be presented here, and the interested reader is referred to this Toxicological Profile for more complete information, as well as an extensive reference list.

A substantial body of literature exists describing the absorption, distribution and metabolism of the PAHs as a group. Unlike many carcinogens, the pharmacokinetic events involved in PAH metabolism and the means by which they initiate carcinogenesis *via* diol epoxide DNA adducts have been intensely researched and are reasonably well characterized (ATSDR, 1995). PAHs express their carcinogenic activity through biotransformation to chemically reactive intermediates that covalently bind to cellular macromolecules such as DNA, leading to mutation and tumor initiation. The products of PAH metabolism include epoxide intermediates, dihydrodiols, phenols, quinones, and their various combinations. The "bay region" diol epoxide intermediates of PAHs are considered to be the ultimate carcinogen for most of the carcinogenic PAHs. These diol epoxides are easily converted into carbonium ions which are alkylating agents and thus mutagens and intiators of carcinogenesis. A prerequisite for conversion of PAHs into these active bay region diol epoxides is the presence of cytochrome P-450 and associated enzymes responsible for this conversion. These are present mainly in the liver, but in lung, intestinal mucosa, and other tissues as well. To some extent, the induction of some of these enzymes can heighten the toxicity of PAHs. In addition, induction of some of these enzymes, such as Aryl Hydrocarbon Hydoxylase (AHH) are known to be under genetic control, meaning that some human genotypes are likely to be more susceptible to PAH-induced cancer. While most of this toxicokinetic work has been done in animals, work in human *in vitro* systems indicates that these same mechanisms of activation may be involved in humans. Although Ph does possess a bay region, and consequently, might be predicted to be a genotoxic carcinogen based on its structure, limited animal experiments and mutagenicity tests have not, as yet, shown this to be the case. ATSDR (1995) has concluded that it is "probable that the bay region on phenanthrene is not very reactive", and that "quantum mechanical calculations indicate a low probability of carbonation formation for the bay region diol epoxide of phenanthrene".

Because of the extensiveness of the documentation in the ATSDR Profile, the only additional relevant citations that will be treated here are those that have been published since that document, or that were not covered by it. The comparative metabolism of phenanthrene in the rat and guinea pig has been treated by Chu *et al.* (1992). Silkworth and coworkers (Silkworth *et al.*, 1995) investigated the immunosuppressive capability of phenanthrene. These investigators found that a single oral dose of 100 mg/kg Ph had little or no ability to suppress antibody response in C57BL/6 mice. Elovaara *et al.* (1995) carried out a dermal and inhalation exposure assessment study for the various PAHs in a group of creosote workers. Breathing zone air measurements were taken for 6 males over five consecutive days. Naphthalene (91-20-3) was the major airborne component, and was the only PAH present as a vapor. Ph was measured as a particulate with geometric mean (geom. S.D) of 3.25 $\mu g/m^3$ (2.01), and with a range from 0.78-10 $\mu g/m^3$ as an eight hour time weighted average (TWA). The concentration of Ph in the creosote itself was 35 $\mu g/mg$. Skowronski *et al.* (1994) investigated the effects of gender, route of administration and soil adsorption on the bioavailability of Ph in Sprague-Dawley rats. They found that bioavailability was higher in females after dermal exposure, and that the compound was eliminated more slowly by females as

well. Moreover, the major urinary metabolite differed between males and females. Although oral absorption was more rapid than dermal, the pattern of metabolism was similar.

Concerning data relevant to carcinogenicity, our searches found reference made to Ph by the International Agency for Research on Cancer (IARC, 1983). The agency concluded that Ph was "Not classifiable as to its carcinogenicity in humans" (Group 3), based on no adequate human data and inadequate evidence in animals. Likewise, EPA has classified Ph as Class D, "Not classifiable as to human carcinogenicity" (EPA, 1994). ATSDR (1995) has reached a similar conclusion. Although the agency has recognized that "evidence exists to indicate that mixtures of PAHs are carcinogenic to humans", they have also noted that the available evidence suggests anthracene and Ph (among other PAHs) "...do not act as complete carcinogens". Moreover, the meagre data available suggest that "phenanthrene was ineffective as an initiator....". However, it should be noted that the studies that are available are either of doubtful quality or used a route of exposure (skin painting, parenteral injection) of questionable relevance to inhalation risk. For this reason, EPA (EPA, 1994) concluded that cancer studies of Ph "are not adequate to assess the carcinogencity of phenanthrene". The studies that are available consist of a single rat gavage study which was negative, five mouse skin painting assays of which four were negative and the fifth (positive) study used benzene as a vehicle, and three parenteral injection studies (one intraperitoneal and two subcutaneous), all of which were negative[1]. IARC (1983) cites one additional mouse skin painting assay, in which Ph was inactive as a promotor.

With respect to mutagenicity data, though test results are somewhat mixed, ATSDR (1995) has suggested the overall findings from genetic toxicology studies do not support the genotoxicity of Ph. Of six test *in vivo* test systems employed in four separate studies, Ph was only weakly positive for sister chromatid exchanges in two studies using Chinese hamster bone marrow. In those cases, the increase over background was <1.5 fold, and comparable doses did not cause chromosomal aberrations, casting doubt on whether the weakly positive result may have been an artifact. *In vitro*, positive results were registered in 8 of 34 tests, with 2 weakly positive results out of 34 when metabolic activation was present. Without metabolic activation, only 2 positive results were recorded out of 39 tests over a variety of test systems (bacteria, fungi, and human and other mammalian cells)[2]. Thus, although data are less than optimal, the available carcinogenicity and mutagenicity data do not adequately support the classification of phenanthrene as a carcinogenic PAH.

The U.S Environmental Protection Agency (EPA) has not published a chronic oral Reference Dose (RfD) or Reference Concentration (RfC) for Ph on its IRIS database (EPA, 1994). IRIS lists an RfC for Ph as being "under review" since 8/4/94. Personal communications[3] with Annie Jarabek and Jeff Gift, U.S. EPA, on 2/18 and 2/19/97 indicated that the previous RfC had been determined to be non-verifiable by the RfD/RfC Workgroup, and that there were currently no plans to develop a new RfC in the forseeable future.

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[1] These studies are discussed in detail in ATSDR, 1995 and EPA, 1994 and will not be repeated here in the interest of brevity.

[2] Endpoints measured in these assays included gene mutations, transformation, mitotic recombination, chromosomal aberrations, sister chromatid exchanges and DNA damage.

[3] These electronic mail communications are documented in the chemical file for Ph.

While not setting a Threshold Limit Value (TLV) for Ph specifically, the American Conference of Governmental Industrial Hygienists (ACGIH) has set a TLV for coal tar pitch volatiles (as benzene solubles) equal to 0.2 mg/m^3 (ACGIH, 1991); this was the basis for the previous interim ITSL. The TLV does not distinguish between known carcinogenic PAHs (such as benzo[a]pyrene (B[a]P), benzo[k]fluoranthene and chrysene) and PAHs for which there is minimal or no evidence of carcinogenicity (such as phenanthrene, acenaphthene and anthracene). ACGIH defines coal tar pitch volatiles subject to the TLV as benzene extractable material which "...contains detectable quantities of benz[a]anthracene, benzo[b]fluoranthene, chrysene, anthracene, B[a]P, phenanthrene, acridine, or pyrene". With little documentation, the justification for setting the TLV at this concentration is stated as follows: "If the concentration of aerosols from coal tar...is maintained below 0.2 mg/m^3, any increase in the incidence of lung and other tumors due to occupational exposure should be minimal". Some anecdotal citations of lung and kidney cancer in laboratory animals, and of lung and pleural cancer in gas workers, coke oven workers and aluminum industry potroom workers are presented as supporting evidence, yet these are qualitative only, and do not appear to provide a clear basis for setting the TLV at 0.2 mg/m^3.

Two health effects/risk assessments for phenanthrene have been published by EPA (EPA 1984, 1982); one of these is specific to phenanthrene (EPA 1984) while the other takes into account several of the other PAHs as well. Unfortunately, neither contains enough specific information to be of appreciable use in the derivation of a screening level. The 1984 report notes that:

> There are no toxicological data that address effects of phenanthrene by either the oral or the inhalation route. ...Data are not available which adequately assess the potential carcinogenicity of phenanathrene. Since no data were available, acceptable intakes or carcinogenic potencies could not be estimated.

Similarly, EPA 1982 concluded that:

> The human effects data for this group of compounds are inadequate to allow a quantitative extrapolation of the human risk associated with environmental exposure to these compounds".

Thus, no adequate long term toxicological data apparently exist which could be used to develop a screening level for Ph. Indeed, even the acute toxicity data cited by RTECS (1996) were unavailable for our review, and could not validated as being of sufficient quality for use in screening level derivation.

Derivation of the ITSL: In choosing data for screening level development, preference is generally given to human epidemiologic data or chronic laboratory animal studies which can be used to derive a Reference Concentration (RfC). Such data were not found in our searches. When adequate data for RfC calculation are not available, next preference is given to oral data for calculation of a Reference Dose (RfD) if available data do not indicate that extrapolation from the oral to the inhalation route of exposure is inappropriate. Currently, no RfD exists for Ph with which to derive a screening level. An oral RfD for the structurally similar PAH anthracene does exist (EPA, 1983); it is set at 0.3 mg/kg body weight-day (300 μg/kg-day). Yet, EPA characterizes their confidence in it and its underlying key study as low. The key study used to derive the

anthracene RfD was a subchronic gavage study which showed no exposure-related effects even at the highest exposure level tested, *i.e.*, the RfD is based on a freestanding No Observed Effect Level (NOEL). Because such studies do not adequately characterize the toxicity threshold, they are often not considered sufficient basis for chronic human health based limits such as the RfD or RfC. In addition, while no comparable data are apparently available for Ph or anthracene, data for other PAHs such as B[a]P suggest that absorption, potency and toxicity following inhalation may differ substantially from that exhibited after oral exposure (ATSDR, 1994). Thus, use of the oral RfD for anthracene as a basis for a screening level for Ph does not appear to be adequately justified.

The next most appropriate alternative would be an ITSL based upon an OEL. As noted above, however, the OEL applicable to Ph is the TLV for benzene soluble coal tar pitch volatiles. The TLV is based upon old data and is less than ideally documented. Moreover, since that TLV is based on prevention of carcinogenic effects, and data available to date suggest that Ph is unlikely to be a carcinogen by the inhalation route of exposure, it is not an appropriate basis for derivation of a screening level either.

Unfortunately, none of the toxicological data specific to Ph and available for our review are adequate for derivation of a screening level. Consequently, per section R 336.1232, rule 232(1)(i) of Act 451, as amended, the **ITSL** for phenanthrene is set to **0.1 µg/m^3**, and per rule 232(2)(c), an **annual averaging** time applies.

In closing, it is strongly recommended that active review of the toxicological literature should be undertaken periodically in the future to identify data upon which to base this screening level. As animal studies or human epidemiological studies of sufficient quality for derivation of an ITSL become available, the derivation of a screening level for Ph should be revisited and an ITSL based upon those established, if appropriate.

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