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Studies Estimating the Dermal Bioavailability of Polynuclear Aromatic Hydrocarbons from Manufactured Gas Plant Tar-Contaminated Soils

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In vitro percutaneous absorption studies were performed with contaminated soils or organic extracts of contaminated soils collected at manufactured gas plant (MGP) sites. The MGP tar contaminated soils were found to contain a group of targeted polynuclear aromatic hydrocarbons (PAH) at levels ranging from 10 to 2400 mg/kg. The soil extracts contained target PAH at levels ranging from 12 000−34 000 mg/kg. Dermal penetration rates of target PAH from the MGP tar-contaminated soils/soil extracts were determined experimentally through human skin using ^{3}H-benzo[*a*]pyrene (BaP) as a surrogate. Results from three MGP sites showed reductions of 2−3 orders of magnitude in PAH absorption through human skin from the most contaminated soils in comparison to the soil extracts. Reduction in PAH penetration can be attributed to PAH concentration and (soil) matrix properties. PAH dermal flux values are used to determine site-specific dermally absorbed dose (DAD) and chronic daily intake (CDI) which are essential terms required to estimate risk associated with human exposure to MGP tar and MGP tar-contaminated soils.

Introduction

Soils contaminated with manufactured gas plant (MGP) tars may contain high concentrations of carcinogenic polynuclear aromatic hydrocarbons (PAH). An estimation of PAH dermal bioavailability from MGP tar-contaminated soils is critical in assessing human health risks associated with dermal exposure. In this study we define dermal bioavailability as the state of being capable of being dermally absorbed and available to interact with the cutaneous and systemic metabolic processes of an organism.

Percutaneous absorption studies using intact human skin is one way to estimate bioavailability in dermal exposures. Percutaneous absorption experiments with a variety of lipophilic materials and, in particular, PAH have demonstrated good correlation between in vivo and in vitro procedures for this class of compounds *(1−4)*. Additionally, in vitro percutaneous absorption using human skin eliminates interspecies extrapolation and overestimates of dermal penetration (relative to humans) often observed with animal models *(5, 6)*. Sorption of PAH on soil can significantly impede their penetration through the skin. Unlike PAH in direct contact with skin, soil-sorbed PAH must first partition from the solid matrix to the outer layer of the skin (stratum corneum or SC) prior to penetration and diffusion. Previous in vitro dermal penetration experiments with individual PAH and PAH in crude oil have demonstrated significant reduction of PAH absorption through human skin when the PAH are sorbed on soil *(7−9)*. The reduction is generally attributed to the presence of soil organic matter; however, neither the earlier studies or the present can adequately measure soil "weathering" or "aging" phenomena which may result in soil-bound chemicals becoming increasingly desorption resistant over time *(10−12)*.

In the present study, in vitro dermal penetration experiments are carried out to determine the dermal penetration properties (flux rates) of PAH in MGP tar-contaminated soils (10−2400 mg/kg PAH) and compare the flux rates with those for the same PAH (12 000−34 000 mg/kg) in the soil extracts. The experimentally measured PAH dermal flux values are then used to calculate the dermally absorbed dose (DAD), an essential component of the equation to determine chronic daily intake (CDI) for quantitative human health risk associated with exposure to MGP tar and MGP tar-contaminated soils.

Background

Chemicals permeate the skin's diffusional barriers and enter the systemic circulation via capillaries at the dermo-epidermal junction (see Figure 1). Percutaneous absorption can be regarded as the translocation of skin surface-applied chemicals through the various strata of the epidermis and a small portion of the underlying dermis that contains papillary capillaries where penetrating substances are first delivered to the blood stream. The dermal flux values determined in the present study are a quantitative measure of systemic uptake of chemical via the dermal route. Percutaneous absorption begins with diffusion through the nonviable stratum corneum. Diffusion through the SC is the rate-limiting step in the percutaneous absorption process for the vast majority of chemicals. Fick's first law of diffusion is used to relate the flux (J) of a chemical through the skin under "infinite dose" (i.e., concentration differential across the membrane equals zero over time), steady-state conditions:

$$J = DK_pC/h$$

where D is the effective diffusion coefficient of chemical in SC, K_p is the partition coefficient of chemical between skin and vehicle, C is the concentration of chemical in vehicle, and h is the effective diffusion path length through the skin barrier.

Flux is directly proportional to chemical concentration and the skin/vehicle partition coefficient. For the special case of contaminated soils, the general term K_p becomes $K_{s/soil}$, the skin/soil partition coefficient.

Assessing potential systemic toxicity with human exposures requires having the ability to experimentally measure

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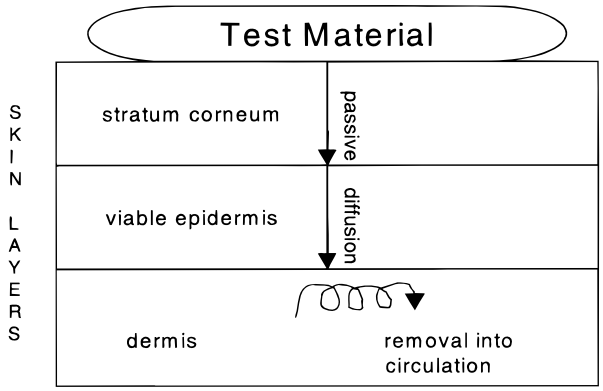

FIGURE 1. Schematic representation of the skin.

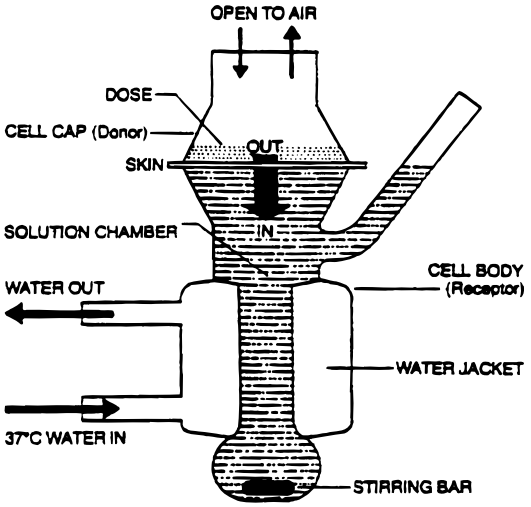

FIGURE 2. Schematic of a static diffusion cell. Soil or soil extract is placed on top of excised human skin and the diffusion of PAH is followed by measuring radioactivity (^{3}H−BaP surrogate) in the receptor fluid over time.

dermal absorption in the laboratory. Dermal absorption is often measured using excised skin (human or laboratory animal) in static diffusion cells such as the one shown in Figure 2. In this experimental setup, diffusion of chemical through skin is measured over time by periodically withdrawing a small amount of receptor solution and determining chemical concentration. Dermal flux is determined by calculating the slope of the plot of cumulative absorption over time.

Experimental Section

Sample Preparation Procedure. Reference soil and study soil samples were prepared based on EPA SW846 (*13*) Method 3550 − sonication/extraction. Method detection limits (MDLs) were determined by spiking clean soil (20 g) with 2.0 mL of a methanolic solution containing 18 target compounds and d12-chrysene (surrogate) prior to sonication. Approximately 2 g of the MGP site soil samples (sieved to particle diameters <150 μm) were extracted. Following the extraction and centrifugation steps, soil sample extracts were concentrated (Kuderna−Danish apparatus) to a 2.0 mL final volume for analysis. Soil extracts provided by META Environmental, Inc. (Watertown, MA) were isolated by Soxhlet extraction.

Sample Analysis Procedure. An internal standard solution was spiked in all samples to attain a final concentration of 20 μg/mL. The standard/sample solutions were analyzed using a Hewlett-Packard gas chromatograph-mass selective detector (GC-MSD) equipped with a J&W (Folsom, CA) DB-5MS fused silica capillary column. The GC-MSD was operated in the selected ion monitoring (SIM) mode. Table 1 lists the 18 target PAH, the deuterated surrogate, and two deuterated internal standards along with the (molecular) ion monitored for qualitative and quantitative analysis.

TABLE 1. Target PAH, Internal Standards/Surrogate and Ion Monitored (*m/z*) for Qualitative and Quantitative Analysis of Soil Extracts

compd	ion monitored (*m/z*)	compd	ion monitored (*m/z*)
naphthalene[a]	128	benz[*a*]anthracene	228
2-methylnaphthalene[a]	142	chrysene	228
1-methylnaphthalene[a]	142	D12-chrysene (surrogate)	240
acenaphthylene	154	benzo[*b*]fluoranthene	252
acenaphthene	152	benzo[*k*]fluoranthene	252
fluorene	166	benzo[*a*]pyrene	252
phenanthrene	178	D12-perylene (I.S.)	264
D10-phenanthrene (I.S.)	188	indeno[1,2,3-*cd*]pyrene	276
anthracene	178	dibenz[*a,h*]anthracene	278
fluoranthene	202	benzo[*g,h,i*]perylene	276
pyrene	202		

[a] Compounds quantitated but not included in determination of "target PAH" dermal flux.

Method Detection Limit (MDL). The MDL is the minimum concentration of an analyte that can be identified, measured, and reported with 99% confidence that the analyte concentration is greater than zero. The MDL was determined by injecting seven prepared 20 g soil extracts at approximately 10 μg/mL (equivalent of 1 mg/kg) with the spiking internal standard at 20 μg/mL. MDLs ranged from 0.12 to 0.46 mg/kg.

Quantitative Analysis. The sample extracts were quantitated based on a five-level calibration curve (1, 5, 10, 20, and 40 μg/mL). The average response factor (RF_{av}) and the relative standard deviation (%RSD) for each of 18 analytes at the five-level calibration standards was calculated using the GC-MSD ChemStation data system EnviroQuant program.

In Vitro Percutaneous Absorption Procedures: Soil Preparation. A total of nine soil samples from three MGP sites were air-dried and presieved to < 150 μm (META Environmental, Inc.) prior to the analytical characterization and dermal absorption experiments. Extracts from the most highly contaminated soil from each site were also prepared for dermal absorption experiments. Any residual, volatile MGP tar components (benzenes, etc.) will be lost during the soil drying and sieving processes. Such compounds are inherently more dermally bioavailable than PAH; however, their concentrations in the native weathered/aged MGP tar-contaminated soil would be negligible and, therefore, not contribute to the human health risk assessment resulting from dermal exposure.

Dose Preparation. Radiolabeled materials used in the study were benzo[*a*]pyrene, [1,3,6-^{3}H] and ^{3}H-water (NEN Research products, Wilmington, DE) with a specific activity of 64 Ci/mmol and 1 mCi/mL, respectively. Soil samples were spiked by first stirring the soil (450 mg) in 5 mL of hexane followed by the addition of 100 μL of a hexane solution of ^{3}H−BaP. A gentle stream of air removed the hexane while the samples were continuously mixed. The resulting air-dried soil was used directly for dermal dosing. Soil extracts were spiked with ^{3}H−BaP and then dissolved in carbon disulfide/acetone (1:1). The final solution (approximately 45 mg extract/100 μL) was used directly for dermal dosing.

Skin Preparation. Experiments were performed using abdominal skin from male and female human cadavers (age

TABLE 2. Recovery of ^{3}H-Benzo[*a*]pyrene upon Completion of the Percutaneous Absorption Experiments

sample/target [PAH][b] (mg/kg)	percent of applied dose[a]				
	receptor fluid	skin[c]	skin wipe	cell rinse	recovery of dose
A150L/14	0.69 (0.1)	0.6 (0.1)	79.8 (4.0)	0.8 (0.3)	92
A150M/140	0.57 (0.2)	0.5 (0.1)	80.5 (2.6)	1.4 (0.3)	83
A150H1,500	0.30 (0.1)	0.6 (0.3)	80.8 (2.6)	0.8 (0.2)	83
A150H-Extract/12 000	1.36 (0.2)	0.7 (0.3)	27.8 (7.8)	63.0[d] (14.6)	93
B150L/10	0.19 (0.1)	1.0 (0.4)	103 (7.7)	1.8 (0.4)	106
B150M/52	0.46 (0.2)	0.9 (0.3)	84.6 (4.7)	2.0 (0.8)	88
B150H/870	0.49 (0.3)	0.9 (0.4)	91.7 (4.4)	3.7 (1.1)	97
B150H-Extract/34 000	2.37 (0.4)	1.8 (0.8)	63.4 (2.3)	33.1[d] (1.1)	103
C150L/38	1.0 (0.4)	0.9 (0.3)	99.4 (1.8)	1.1 (0.2)	102
C150M/170	0.53 (0.1)	0.4 (0.1)	88.8 (6.1)	1.2 (0.2)	91
C150H/2,400	0.2 (0.1)	0.7 (0.3)	89.7 (6.4)	2.9 (1.6)	94
C150H-Extract/32 000	6.5 (2.6)	2.5 (0.7)	30.2 (13.6)	59.2[d] (14.3)	98

[a] Results are expressed as the mean (standard deviation) of 4−5 diffusion cells per experiment. [b] A, B, and C indicate MGP sites A, B, and C; 150 = <150 μm soil particle size; L, M, H = low, mid, and high concentration soil. [c] Skin = activity recovered after wiping skin surface (removal of dose). [d] Dose removed from skin surface with cell cap (material in contact with the skin).

range was 31−88 years) procured from the National Disease Research Interchange (NDRI) in Philadelphia, PA. Whole skin sections were stored frozen. Skin sections were shaved (as necessary) prior to using a Padgett dermatome (Kansas, MO) equipped with a No. 252 blade to slice skin sections (epidermis side) to approximately 350 μm. Prepared skin sections were vertically cut into 3 × 3 cm sections and their thicknesses measured with a pressure sensitive micrometer. Each section was then mounted over a 15 mm diameter Franz diffusion cell body and a Teflon O-ring and cell cap placed atop the skin and secured with an adjustable clamp.

Dermal Absorption Procedure. The diffusion cells were contained in a Franz diffusion unit (Crown Glass, Somerville, NJ). An aqueous solution of 6% polyethylene glycol 20 oleyl ether (Volpo-20) and 0.01% thimerosal antibacterial agent was used as receptor fluid. Temperature of the diffusion cells was maintained at 37 °C by attaching water-jacketed cells to circulating water baths. Integrity of the human skin sections was evaluated with ^{3}H-water before use; only sections exhibiting normal water permeation ($k_p < 1.0 \times 10^{-2}$ cm/h) were used for studies. Mounted skin sections were dosed at approximately 45 mg of soil/diffusion cell or 25 mg of soil/cm^2 for 144 h experiments ($n = 5$ cells/experiment); high concentration soil extracts were applied by volume (100 μL final volume), and the solvent immediately evaporated with a gentle stream of air. Receptor fluid was sampled (200−400 μL) at 1, 3, 5, 7, 24, 48, 72, 96, 120, and 144 h post-dose. At termination, the remaining dose was removed from skin surface by wiping with corn oil-wet and dry cotton applicators.

Radioactivity was quantitated on a Beckman liquid scintillation counter following standard operating procedures including external calibration and sample quench determination. Dermal flux rate (mass of PAH/cm^2 skin surface/h) was calculated from linear regression of receptor fluid activity at each time point for each cell. Dermal flux rates reported are derived from the best fit linear portion of absorption curves. Soil experiments used 7 to 96 h data points, while soil extract was calculated from 0 to 7 h.

Results and Discussion

In vitro dermal penetration is summarized in Table 2. Mass-balance (recovery of dose) of radioactivity ranged from 83 to 106% of applied dose for 12 experiments. The percentage of activity recovered in receptor fluid and in skin is often referred to as percent of applied dose absorbed (PADA). In the present study, PADA is very small compared to the applied dose; generally however, PADA values reported in the literature can range significantly depending upon amount of applied dose. It has been predicted and observed that PADA is inversely proportional to dermally applied dose or so-called soil load on skin. Yang et al. *(1)* found PADA for benzo[*a*]pyrene increased in an inversely proportional manner when the soil load was decreased from 56 to 9 mg/cm^2, demonstrating a constant mass flux within loading range. Kissel and McAvoy *(14, 15)* used a fugacity-based modeling approach to evaluate 2,3,7,8-TCDD dermal bioavailability from soil and predicted increases in PADA with decreasing soil load assuming uniform coverage of the skin surface. Duff and Kissel *(16)* reaffirmed the observations of Yang et al. and the predictions of Kissel and McAvoy. Dermal exposure protocols that fail to account for dependence of PADA on soil loading can result in inaccurate estimates of dermal exposure and inaccurate human risk assessments.

Difficulties inherent to PADA are avoided by conducting in vitro dermal penetration experiments under infinite (nonlimiting) dose conditions. The 25 mg/cm^2 of soil or soil extract dose used in this study is essentially an inexhaustible supply of measured PAH which permits measurement of dermal flux (J) of the target PAH from soil or soil extract under steady-state conditions. Figure 3 shows a representative plot of mass (target PAH) diffused through human skin over time for one soil (Figure 3a) and soil extract (Figure 3b) examined in the study. Significant differences in slopes were observed between all soils and soil extracts. Soil plots are characterized by a slow, linear (steady-state) absorption over the time course of the experiment. Soil extract plots reflect an initial rapid penetration of PAH into the receptor fluid within the first few hours followed by a somewhat slower penetration rate following solidification of the extract. Linear regression statistics were used to determine best fit of data over the linear (infinite dose/steady state) portion of the absorption curves. Data from the initial (liquid) phase of the soil extract absorption curve was used in the regression analysis since it was felt that this better represented a potential human exposure (e.g., 8-hour workday) scenario. The resultant slopes represent estimated dermal flux (J) for target PAH from the respective medium.

Flux values are based on measurement of ^{3}H−BaP, which is used as a surrogate for the target PAH. Evaluation and use of BaP or other homologues as surrogates for PAH has been reported by several groups. Roy et al. *(17)* evaluated dermal penetration of 27 PAH through rat skin and found that the absorption rate of all the 4−6 ring PAH studied fell within a factor of 2 of BaP. In a refinement of the same work with 60 PAH *(18)*, approximately 40 of 60 PAH tested showed dermal flux rates within a factor of 2 of BaP, and 55 of 60 showed rates within a factor of 3. Dankovic et al. *(19)*

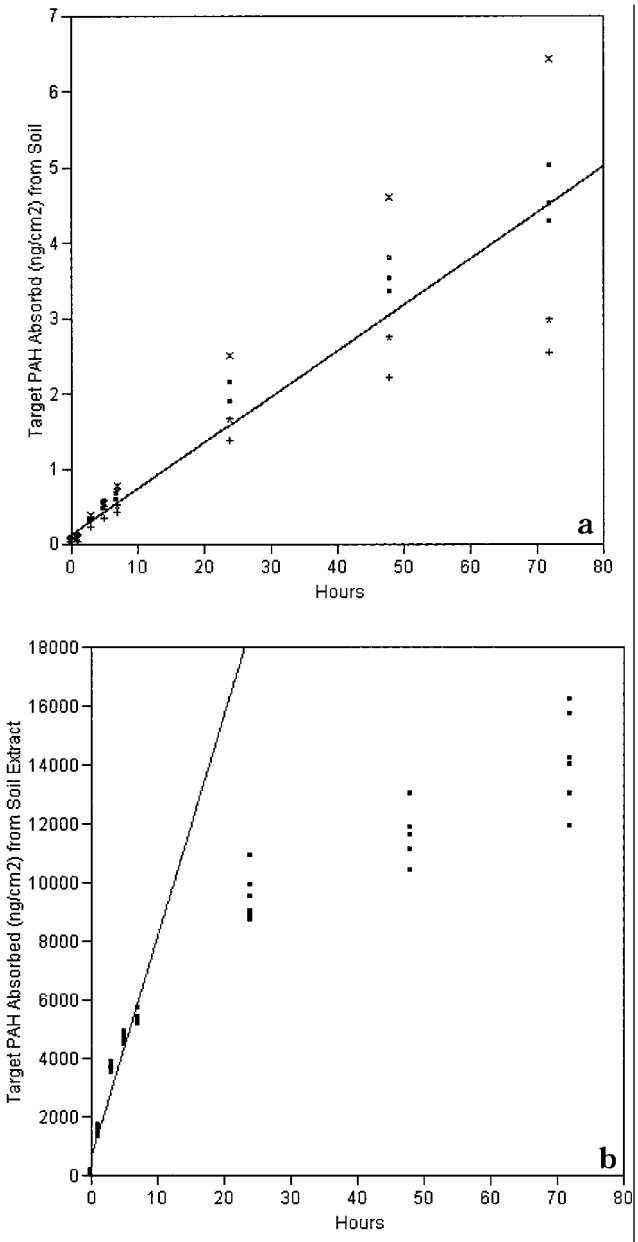

FIGURE 3. Plot of mass (target PAH) diffused through human skinover time from (a) contaminated soil and (b) contaminated soil extract. The mean (n = 5 diffusion cells) regression line slope = dermal flux = 0.059 ng/cm²/h for soil and 750 ng/cm²/h for soil extract).

studied dermal penetration of BaP in relation to a group of 12 other PAH in vivo (mouse). Dermal half-life of the PAH ranged from 5.0 to 8.8 h with BaP having a half-live of 6.7 h. Dankovic concluded that BaP is a reasonable choice to use as a representative PAH marker compound for studies of mixture effects on dermal penetration of four- and five-ring PAH.

Figure 4 compares dermal flux values for target PAH from MGP tar-contaminated soils and extracts of high concentration MGP tar soils from three MGP sites. Dermal flux values for MGP tar-contaminated soils ranged from 6.4×10^{-3} ng/cm²/h to 2.2 ng/cm²/h over the range of PAH contamination (10−2400 mg/kg). PAH dermal flux values for high PAH concentration soil extracts ranged from 210 to 750 ng/cm²/h. The data show that sorption on soil retards the dermal penetration rate of target PAH by a factor of 160−900 for high concentration range soils.

Reduction in PAH dermal absorption rates from soils as compared to soil extracts is attributable to differences in

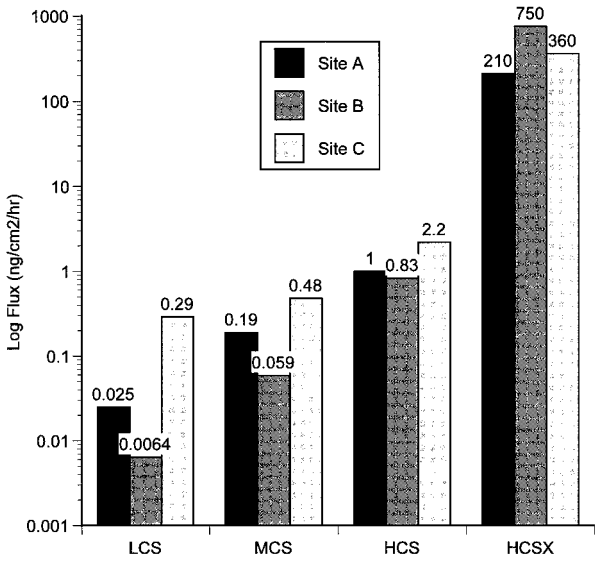

FIGURE 4. Comparison of target PAH (log) dermal flux rates (human skin) from low (LCS), medium (MCS), and high concentration (HCS) MGP coal tar-contaminated soils and high concentration soil extracts (HCSX).

TABLE 3. Experimentally Determined (Mean) Dermal Flux (J) Rates and Calculated Dermally Absorbed Dose (DAD) Values for Target PAH in MGP Tar-Contaminated Soils and Soil Extracts

sample description[a] target [PAH] (mg/kg)	dermal flux (J) rate[b] (ng/cm²/h)	dermally absorbed dose (DAD) (mg/kg/day)
A150L/14	0.025 (0.21)	2.3 E-6
B150L/10	0.0064 (0.22)	6.0 E-7
C150L/38	0.29 (0.43)	2.7 E-5
A150M/140	0.19 (0.26)	1.8 E-5
B150M/52	0.059 (0.37)	5.5 E-6
C150M/170	0.48 (0.23)	4.5 E-5
A150H/1500	1.0 (0.35)	9.4 E-5
B150H/870	0.83 (0.51)	7.8 E-5
C150H/2400	2.2 (0.53)	2.0 E-4
A150H-EXT/12 000	210 (0.19)	2.0 E-2
B150H-EXT/34 000	750 (0.52)	7.1 E-2
C150H-EXT/32 000	360 (0.34)	3.4 E-2

[a] A, B, and C indicate MGP sites A, B, and C; L, M, H and EXT = low, mid, and high concentration soil and soil extract. [b] Values are the mean flux from 4−5 individual skin sections tested and are reported with the relative standard deviation (RSD).

PAH concentration (by virtue of Fick's first law of diffusion) and soil matrix binding effects. Flux values normalized for differences in concentration between soils and extracts (see A-C150H and A-C150H-EXT, Table 3) reveal the magnitude of PAH soil matrix binding. In the studies described here, skin penetration rate reductions of 26-, 23-, and 12-fold (i.e., for A-C150H vs A-C150H-EXT) can be attributed to soil binding effects. These rate reductions are, undoubtedly, conservative since they reflect only the immediate (≤ 24 h post-dose preparation) reduction in PAH bioavailability (as measured by ^{3}H−BaP) observed by merely adding (lipophilic) compounds to soil. The rates do not reflect the additional reduction in bioavailability of the contaminant PAH expected as a result of aging or, more specifically, physical and/or chemical sequestration *(10−12)*. For the highly contaminated soils examined here, the reduction in PAH skin penetration rates due to soil sorption is of the same order of magnitude as the reduction in rate due to lower concentration (compared to soil extracts). Variability in soil sorption has been attributed to soil composition and, in particular, soil organic content *(20, 21)*.

Flux values for PAH in MGP tar-contaminated soils can be directly used for dermal exposure assessment and risk assessment at MPG tar sites. Determination of DAD that is required to calculate the risk associated with exposure to MGP tar-contaminated soils and MGP tars can be based on the procedures described in EPA Interim Report: Dermal Exposure Assessment − Principal and Applications *(6)*:

$$DAD = DA \times EF \times ED \times A/(BW \times AT)$$

where DAD = dermally absorbed dose (mg/kg/day), DA = dose absorbed per exposure (mg/cm^2/day), EF = exposure frequency (days/year), ED = exposure duration (years), A = exposure surface area (cm^2), BW = body weight (kg), and AT = average time (days).

For carcinogenic effects of PAH present in MGP tar, the following estimates or default values are used: DA = dermal flux rate (mg/cm^2/hour) × 8 h/day, EF = 350 days/year, ED = 30 years, A = 2000 cm^2 (head and hands), BW = 70 kg, AT = 70 years or 25 550 days.

Since a number of PAH often found in MGP tars are classified by EPA as B2 carcinogens (i.e., probable human carcinogens), a value for average time (AT) of exposure is 70 years. All other variables are conservatively set at EPA-recommended default values. Exposure surface area (A = 2000 cm^2) is considered a typical case for worker exposure. Only dose absorbed per exposure (DA_{event})—which is derived directly from the experimentally measured dermal flux rate—varies in these calculations. Accordingly, the range of calculated DAD-values for MGP tar-contaminated soils and extracts (Table 3) covers 5 orders of magnitude, reflecting range of measured PAH penetration rates in this study. These site-specific DAD values for target PAH in MGP tar-contaminated soils and soil extracts provide the essential dermal exposure term required for calculating CDI and the risk associated with dermal exposure to MGP tar-contaminated soils.

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