Relative Absorption Factors (RAFs) for Oral and Dermal Absorption of Compounds in Soil Cabot Carbon/Koppers Site Gainesville, Florida

Prepared by:

AMEC Earth & Environmental, Inc.
Westford, Massachusetts

July 23, 2008

1.0 General Background

To estimate the potential risk to human health that may be posed by the presence of compounds in various environmental media (such as soil, sediment, water or air), it is necessary to both estimate the potential exposure to a compound and have information about the potential toxicity the compound. In most human health risk assessments potential exposure is estimated as the human exposure dose of each compound. The exposure dose is similar to the administered dose or applied dose of a laboratory experiment. The exposure dose is then combined with an estimate of the toxicity of the compound to produce an estimate of risk posed to human health.

The estimate of toxicity of a compound, termed the dose-response value, can be derived from human epidemiological data, but it is most often derived from experiments with laboratory animals. The dose-response value can be calculated based on the administered dose of the compound (similar to the human potential dose) or, when data are available, based on the absorbed dose, or internal dose, of the compound.

In animals, as in humans, the administered dose of a compound is not necessarily completely absorbed. Moreover, differences in absorption exist between laboratory animals and humans, as well as between different media and routes of exposure. Therefore, it is not always appropriate to directly apply a dose-response value to the potential human exposure dose. In many cases, a correction factor in the calculation of potential risk is needed to account for differences between absorption in the dose-response study and absorption likely to occur upon human exposure to a compound. Without such a correction, the estimate of potential human health risk could be over- or under-estimated.

This correction factor is termed the absorption adjustment factor (AAF) or relative absorption factor (RAF). The RAF is used to adjust the human potential dose so that it is expressed in the same terms as the doses used to generate the dose-response curve in the dose-response study. The RAF is the ratio between the estimated human absorption factor for the specific medium and route of exposure, and the known or estimated absorption factor for the laboratory study from which the dose-response value was derived.

RAF = (fraction absorbed in humans for the environmental exposure)/
(fraction absorbed in the dose-response study).

The use of an RAF allows the risk assessor to make appropriate adjustments if the efficiency of absorption between environmental exposure and experimental exposure is known or expected to differ because of physiological effects and/or matrix or vehicle effects. Relative absorption factors can be less than one or greater than one, depending on the particular circumstances at hand. If it is thought that absorption from the site-specific exposure is the same as absorption in the laboratory study, then the RAF is 1.0.

2.0 Application to the Cabot Carbon/Koppers Inc Site in Gainesville, Florida

Deterministic and probabilistic risk assessments will be performed at the Cabot Carbon/Koppers Inc. site in Gainesville, Florida (Site), to evaluate the potential human health risks associated potential exposures to Site-related constituents. Based upon past experience at other wood treating sites, it is expected that the human health risk

assessment for the Cabot Carbon/Koppers Inc Site will include assessment of the potential human health risks associated with oral and dermal exposures to soils containing polycyclic aromatic hydrocarbons (PAHs), 2,3,7,8 tetra-chlorosubstituted dioxins and furans (2,3,7,8-TCDD-TEQ), and arsenic. RAFs are proposed for these constituents in the human health risk assessment for this Site. Quantitative estimates of potential risk associated with other constituents may also be included in the human health risk assessment. RAFs may be proposed for these other compounds as well but because their identity will not be known until the human health risk assessment is initiated, RAFs for other compounds are not presented herein. They will be presented in the human health risk assessment.

AMEC has critically reviewed the available peer-reviewed scientific publications that present information on the relative absorption of each of these constituents from soil, identified those RAFs that are applicable to the Site, and reviewed their overall distribution to generate a conservative estimate of the expected relative bioavailability of each constituent. As shown below, there is strong evidence that the relative absorption of each of these constituents from soil is less than EPA's default assumption of 1.0. However, to ensure that potential risks are not underestimated, AMEC is proposing to use conservative point estimates for RAFs in the deterministic risk assessment of PAHs and TCDD (i.e., the 90th percentile of the distribution of RAFs) and the full distribution of RAFs in the probabilistic risk assessment of PAHs and TCDD. In the case of oral exposures to arsenic, we have identified an RAF derived from soils at a wood treating site in Gainesville and propose to use that RAF in the deterministic assessment. That same study presents RAFs for five sites in Florida. We propose to use the distribution of RAFs from that study in the probabilistic assessment. For dermal exposures to arsenic in soil, AMEC proposes to use the 90th percentile values from the literature for the deterministic assessment and the full distribution for the probabilistic assessment.

Following is a summary of the RAFs for PAHs, 2,3,7,8-tetrachlorosubstituted dioxins and furans, and arsenic.

3.0 PAHs

AMEC has summarized the route of exposure and the experimental matrix (diet, drinking water, corn oil gavage, etc.) used in the experimental study from which the relevant dose-response value was derived for each PAH compound. In addition, AMEC has reviewed scientific literature on the absorption and bioavailability of PAH for the relevant routes of exposure and matrices. Based on these data, AMEC has derived a scientifically defensible distribution of RAFs for each relevant group of PAHs (cancer or noncancer)/route/medium situation.

3.1 Absorption in Dose-Response Studies

Absorption was not measured in the laboratory studies used to develop toxicity factors. Therefore, it was necessary to identify the dosing methods used in the toxicity reference studies and then to look to other studies of the absorption of PAH for those particular methods.

Potentially carcinogenic PAH are routinely evaluated using the comparative potency approach described in U.S. EPA (1993). With this approach, all potentially carcinogenic

PAH are assessed in terms of their benzo(a)pyrene toxic equivalent concentrations, and U.S. EPA's cancer slope factor for benzo(a)pyrene is used.

The risk assessment of potentially carcinogenic PAHs is performed using the oral cancer slope factor (CSF) for benzo(a)pyrene (B(a)P). The oral CSF for B(a)P (7.3 $(mg/kg\text{-}day)^{-1}$) is the geometric mean of four slope factors derived from two rodent feeding studies: Neal and Rigdon (1967) and Brune *et al*. (1981). In the first study, CFW mice were dosed with B(a)P in their laboratory chow (diet). The diet was prepared by dissolving benzo(a)pyrene in benzene, mixing with wheat flour, evaporating the benzene and mixing the flour-benzo(a)pyrene mixture with laboratory chow pellets. In the second, Sprague Dawley rats were also dosed with B(a)P in their laboratory chow (diet).

The oral RfD for anthracene was derived from a 90 day corn oil gavage study in male and female CD-1 (ICR) BR mice. The mice were given 250 to 1000 mg/kg-day for at least 90 days. The RfD is reported as 0.3 mg/kg-day (U.S. EPA 2008).

The oral RfD for fluoranthene was derived from a 13 week corn oil gavage study in male and female CD-1 mice. The mice were given 125 to 500 mg/kg-day. The RfD is reported as 0.04 mg/kg-day (U.S. EPA 2008).

The oral RfD for fluorene was derived from a 13 week corn oil gavage study in mice. The mice were given 125 to 250 mg/kg-day. The RfD is reported as 0.04 mg/kg-day (U.S. EPA 2008).

The oral RfD for pyrene was derived from a 13 week corn oil gavage study in male and female CD-1 mice. The mice were given 75 to 250 mg/kg-day. The RfD is reported as 0.03 mg/kg-day (U.S. EPA 2008).

The oral RfD for naphthalene was derived from a 13 week corn oil gavage study in rats (NTP, 1980). The rats were given 25 to 400 mg/kg-day. The RfD is reported as 0.02 mg/kg-day (U.S. EPA 2008).

Thus, studies of dosing by diet and gavage are of interest in determining the absorption relevant to PAH toxicity factors.

Absorption of B(a)P and other PAHs from food has been shown to be high in both humans and rodents by several researchers. Many articles on absorption were reviewed. However, studies that used inappropriate scientific methods were rejected for RAF derivation. For instance, studies that measured total radiolabel in the feces do not yield useful absorption information, because B(a)P metabolites are known to be excreted into bile (see, for instance, Chipman *et al*., 1981a, 1981b; Bowes and Renwick, 1986) and therefore absorbed material would also appear in the feces.

As an example, data are presented in a paper by Chang (1943) on fecal excretion of benzo(a)pyrene and other PAH. This paper cannot be used to estimate gastrointestinal absorption of PAH, because the gravimetric analytical method used is nonspecific and does not distinguish between unchanged PAH and PAH metabolites. A paper by Flesher and Syndor (1960) is also deficient for RAF derivation, because total tritium is measured in feces after oral dosing of rats with ^{3}H-3-methylcholanthrene. This method does not distinguish between unabsorbed PAH and absorbed and metabolized PAH

excreted into the bile and feces.

Other studies are not useful because they only define a small fraction of a PAH's total disposition. For instance, in a study by Rees *et al.* (1971), benzo(a)pyrene was given to rats by stomach tube and the PAH was measured in the lymphatic duct. While the presence of B(a)P in the lymph indicates that absorption occurred, the experiment is not quantitative. Similarly, Foth *et al.* (1988) measured benzo(a)pyrene absorption in the rat after a continuous infusion into the duodenum by measuring B(a)P in the atrial blood and bile. In this case, the conditions of the experiment are unnatural, and the experiment does not account for a total mass balance of B(a)P. Other studies were rejected for similar reasons. The following principal studies are those in which useful absorption quantitative information can be determined.

Hecht, et al. (1979)

Hecht and coworkers (Hecht *et al.,* 1979) fed B(a)P to both humans and F-344 rats and measured the unchanged B(a)P in the feces to obtain an estimate of the amount of the compound absorbed. Because unchanged B(a)P in the feces can be due to absorbed material that is excreted unchanged in the bile, these studies reveal the minimum amount of B(a)P that was absorbed. It is known, however, that B(a)P is extensively metabolized, so that the potential underestimate of absorption caused by biliary excretion of B(a)P is minor. Thus, these estimates of absorption are valid for RAF derivation.

For rats, at least 87% of B(a)P was absorbed from a low single dose in peanut oil (0.037 mg/kg). Minimum absorption from medium and high doses (0.37 mg/kg and 3.7 mg/kg) were 92.2% and 94.4%. The mean absorption of B(a)P in peanut oil in rats was 91.2% (n=30). This value was used in RAF derivation.

When rats were fed a single dose of charcoal-broiled hamburger containing B(a)P (0.002 mg/kg body weight), at least 89% was absorbed (n=10). In humans, a high percentage of B(a)P present in charcoal-broiled meat was also absorbed (0.0001 mg/kg body weight, assuming 70 kg), because no unchanged B(a)P was detected in the feces. Assuming that B(a)P was present in feces at 1/2 the detection limit, the minimal absorption is 98.8% (n=8). This study indicates that there is no significant difference in absorption between two dietary vehicles in rats. That is, absorption of B(a)P from peanut oil and meat was essentially the same. The results with rats and humans also indicates that there is no major difference in the gastrointestinal absorption of B(a)P between rats and humans when administered in food items. Both of the above values were used in RAF derivation.

Mirvish, et al. (1981)

Mirvish and co-workers (Mirvish, e*t al*., 1981) fed B(a)P to Syrian golden hamsters in their diets and measured the amount of unmetabolized B(a)P in their feces to determine the efficiency of absorption from the gastrointestinal tract. In method I, a B(a)P solution in 150 ml acetone was pipetted onto 1 kg pelleted diet contained in a glass bottle, with occasional gentle shaking. The pellets were dried overnight on trays. This method of preparing a B[a]P-containing diet is the same as the method used in the Neal and Rigdon (1967) study from which the cancer slope factor was derived. In Method II, B(a)P

was dissolved in corn oil, and the corn oil was added to a commercial rodent chow. Animals were treated with B(a)P in the diet for 7 to 10 days before samples were collected to give adequate time to reach steady-state PAH concentrations in the feces and gastrointestinal tract contents.

The percentage of fecal excretion of unchanged B(a)P remained relatively constant (94.3% to 98.0%) as its concentration in commercial diet was varied over a wide range (0.16 mg/kg to 5.5 mg/kg). Absorption efficiency was not dose-dependent. The minimal gastrointestinal absorption of B(a)P was found to be 96.7% for the commercial chow using preparation method I (average of results from seven experiments at different dose levels; eleven animal groups, each containing 3-5 hamsters) or 98% for the commercial chow using preparation method II (one experiment; four animal groups, each containing 3-5 hamsters, 1.6 mg/kg). These two values (96.7% and 98%) were used in RAF derivation.

3-methyl cholanthrene (3-MC) absorption was also studied in hamsters. 3-MC (1.7 mg/kg) was dissolved in corn oil and added to a semisynthetic diet consisting of corn oil, corn starch, vitamin-free casein, and alphacel. Minimum gastrointestinal absorption was found to be 93.8% in four animal groups containing 3-5 hamsters each. This value is also used in RAF derivation.

Other experiments demonstrated that B(a)P was absorbed slightly more efficiently from semisynthetic diets than from commercial rodent diets. Addition of corn oil to the hamsters' semisynthetic diets had little effect on the fecal excretion of unchanged B(a)P, and thus its gastrointestinal absorption. Addition of bran to the semisynthetic diets caused a slight lowering of gastrointestinal absorption.

Rabache, et al. (1985)

Rabache and co-workers (Rabache, *et al*., 1985) fed B(a)P to male Wistar rats in their diets for 22 days and measured the amount of unmetabolized B(a)P in their feces to determine the efficiency of absorption from the gastrointestinal tract. B(a)P was dissolved in soy oil and mixed with the synthetic ration, which was comprised of 10% soy oil. Young rats were given 1 g B(a)P/kg body weight, and adult rats were given 5 g/kg. The minimal gastrointestinal absorption of B(a)P was found to be 88.7% for young rats (n=8) and 99.6% for adult rats (n=12). Both of these values are used in RAF derivation.

Withey, et al. (1991)

Withey and co-workers (Withey, *et al*., 1991) administered pyrene by stomach tube to male Wistar rats in an aqueous emulsion and measured the amount of C-14 radiolabel in the blood over time to make an estimate of the traditional pharmacokinetic parameter "bioavailability". A single dose of pyrene was given to 4 groups of six animals at a concentration ranging from 4-15 mg/kg as a solution in 20% Emulphor/80% physiological saline. Radiolabeled pyrene was also given intravenously for comparison. "Bioavailability" was defined as the area of the blood level-time curve of radiolabel over a specified time period after oral dosing (0-8 hours) divided by the corresponding area of the curve for intravenous dosing.

"Bioavailability" was found to vary from 65% to 84% depending on dose level. This

pharmacokinetic parameter has its basis in classical drug studies where the circulating blood level of the parent (unmetabolized) drug is of primary interest. However, this parameter does not provide an optimal estimate of a chemical's gastrointestinal absorption, because the fraction of the chemical or its metabolites that leaves the blood and distributes to tissues is not properly counted.

For this reason, the urinary excretion data over 6 days were also used to derive an estimate of absorption for each group. Absorption was estimated as the fraction of total radiolabel excreted in the urine after oral dosing divided by the fraction excreted after intravenous dosing. Because the fraction excreted in the urine at day 6 post-dosing was slightly higher at every dose level for oral dosing compared to intravenous dosing, the estimates of gastrointestinal absorption are 100% for all four dose groups.

For each dose group, the blood level estimate of "bioavailability" was averaged with the urinary estimate of gastrointestinal absorption to derive an estimate of gastrointestinal absorption. These estimates are: 92%, 82.5%, 86.5%, and 87% for doses ranging from 4-15 mg/kg. The average of these four estimates (87%) is used in RAF derivation.

Grimmer, et al. (1988)

Grimmer and co-workers (Grimmer, *et al*., 1988) administered chrysene by stomach tube to unfasted male Wistar rats in a solution of 33% dimethylsulfoxide and 66% corn oil. Eight rats weighing 200-250 grams received a single dose of 50 ug chrysene. Assuming an average weight of 225 g, the dose was 0.22 mg/kg. Feces and urine were collected for four days. Unchanged chrysene and specific metabolites were analyzed. The fraction of the unchanged chrysene in the feces was determined. This serves as an estimate of minimal gastrointestinal absorption. Average absorption for the eight rats was 86.9%. This value was used in RAF derivation.

Bartosek, et al. (1984)

Bartosek and co-workers (Bartosek, *et al*., 1984) administered benz(a)anthracene, chrysene, or triphenylene to female CD-COBS rats by stomach tube in an aqueous emulsion of 10% Pluronic F68 emulsifier and 90% olive oil. Animals were fasted for 24 hours prior to being given a single oral dose of the PAH. Each group consisted of 3-5 rats weighing 150-170 g. PAH were given at single doses of 11.4 and 22.8 mg/ animal, which correspond to 71.3 mg/kg and 142.5 mg/kg, assuming an average weight of 160 g. Rats were allowed access for food 3 hours after dosing. The fraction of administered dose of the unchanged PAH recovered in the feces after 72 hours was taken as an estimate of the minimal absorption. Results were 94% for benz(a)anthracene, 75% for chrysene, and 97% for triphenylene. These three values were used in RAF derivation.

Summary of Absorption Data for Exposure Methods used in the Dose-Response Studies

The data presented above and summarized in Table 1, indicate that, although there is some variability in the absorption of various PAH, no consistent trend is apparent that would lead one to conclude that absorption of one PAH differs significantly from another when administered in the ways used to derive dose-response data. In addition, the data show that gastrointestinal absorption of PAH is relatively high, whether given in oil vehicles or in the diet. Accordingly, all of the data from the dose-response studies from

which the cancer slope factor for B(a)P and the RfDs for various noncarcinogenic PAH were derived, were merged to derive an absorption estimate for all PAHs of interest. The resulting estimate of gastrointestinal absorption of PAH is 92%.

However, each data point in a study was not given equal weight in deriving the final estimate of oral absorption in the dose-response studies. For instance, in the Mirvish, *et al.* study the 96.7% value represents the average of results from seven experiments at different dose levels. There were eleven animal groups, each containing 3-5 hamsters. Thus, this value represents experiments with 33-55 animals. The 98% value represents one experiment at one dose group. There were four animal groups, each containing 3-5 hamsters. Thus, this data point represents 12-20 animals. There are many ways to summarize such a large and diverse set of experimental results. Table 2, however, demonstrates that the resulting estimate of absorption in the PAH dose-response studies is not particularly sensitive to the manner of summarizing the available data.

TABLE 1
SUMMARY OF ABSORPTION DATA FOR PAH DOSE-RESPONSE STUDIES

Value	Citation	Animal	PAH	Vehicle
91.2%	Hecht	male F344 rats	B(a)P	Peanut oil (single dose)
89%	Hecht	male F344 rats	B(a)P	Char-broiled hamburger (single dose)
98.8%	Hecht	Humans	B(a)P	Char-broiled hamburger (single dose)
88.7%	Rabache	young male Wistar rats	B(a)P	Synthetic diet + soy oil (22 days)
99.6%	Rabache	adult male Wistar rats	B(a)P	Synthetic diet + soy oil (22 days)
96.7%	Mirvish	male Syrian golden hamsters	B(a)P	Commercial Diet Method I (7-10 days)
98.0%	Mirvish	male Syrian golden hamsters	B(a)P	Corn oil + commercial diet Method II (7-10 days)
87%	Withey	male Wistar rats	pyrene	20% Emulphor/ 80% saline (single dose)
86.9%	Grimmer	male Wistar rats	chrysene	33% DMSO/ 66% corn oil (single dose)
94%	Bartosek	female CD-COBS rats	B(a)A	10% emulsifier/ 90% olive oil (single dose)
75%	Bartosek	female CD-COBS rats	chrysene	10% emulsifier/ 90% olive oil (single dose)
97%	Bartosek	female CD-COBS rats	triphenylene	10% emulsifier/ 90% olive oil (single dose)
93.8%	Mirvish	male Syrian golden hamsters	3-methyl cholanthrene	Corn oil + semisynthetic diet (7-10 days)

TABLE 2
METHODS OF SUMMARIZING PAH GASTROINTESTINAL ABSORPTION DATA

Method Used	# Data Points	Average Absorption
Each experiment within a study used as a single data point*	13	92.0%
Each result presented in each study used as a single data point	24	92.1%
Each result presented in each B(a)P study used as a single data point	15	95.0%
Each study represented as a single data point	7	90.9%
Each B(a)P study represented as a single data point	3	94.4%

* Method used in this RAF derivation.

3.2 RAF for Oral Exposure to Soil

Seven studies were identified in which the gastrointestinal absorption of PAHs was measured from a soil matrix. These include Goon, *et al.* (1991), Goon, *et al.* (1990), Weyand, *et al.* (1996), Magee, *et al*. (1999), Koganti, *et al* (1998), and Bordelon, *et al*. (2000), and Grøn, *et al*. (2007). Each of these studies is discussed below. Each of these studies used exposure methods similar to those employed in the dose-response investigations (feeding or gavage) and, additionally, had their own internal controls. Therefore, RAFs may be calculated directly from the work, without use of fractional absorption observations noted in the studies described previously.

Studies

Weyand, et al. (1996)

Weyand, *et al.* (1996) studied the bioavailability of pyrene from manufactured gas plant (MGP) residue (coal tar) by comparing the urinary pyrene metabolite levels in animals receiving pyrene as methylene chloride extracts of MGP contaminated soil in their diet to animals receiving pyrene as MGP contaminated soil in their diet. The two contaminated soil samples were aged soils from MGP sites. They were sieved to a particle size range of less than or equal to 0.150 mm. Soil was added to powder diets from PMI Feeds, Inc. (rodent laboratory diet #5001) (20% soil / 80% powder diet). MGP contaminated soil extracts were added to gel diets from Bio-Serv (rodent basal gel diet) so that the same amount of pyrene was present as in the soil/diet groups. Groups of female $B_6C_3F_1$ mice were fed soil or organic extract for 14 days. Urine was collected on day 14. The level of pyrene metabolites (1-hydroxypyrene, 1-hydroxypyrene glucuronide conjugates, and 1-

hydroxypyrene sulfate conjugates) were determined by HPLC using fluorescence detection (Singh, *et al*., 1995).

“Fractional urinary excretion" is defined as the amount of pyrene excreted in the urine over 24 hours on day 15 divided by the amount of pyrene ingested on day 15 x 100. The amount of pyrene excreted into the urine is not, itself, a direct measure of total absorption of pyrene from the diet, because PAH are efficiently excreted into the feces via the biliary system. However, the level of pyrene and its metabolites in urine on day 15 gives a measure of the steady state level of pyrene excretion.

As shown in Table 3, the "fractional urinary excretion" of pyrene from soil #1 was 6.2% and from soil #2 was 1.7%. The "fractional urinary excretion" of pyrene from the organic extract of soil #1 was 17.2% and from soil #2 was 16.1%.

The ratio of "fractional urinary excretion" from MGP contaminated soil to "fractional urinary excretion" from an extract of MGP contaminated soil added to diet is a direct estimate of the oral-soil RAF. It is a measure of the degree to which the presence of soil increases or decreases the absorption of pyrene from the diet. The RAF from soil #1 was 36% (6.2%/17.2% x 100).

TABLE 3
PYRENE URINARY METABOLITES, SOIL VS ORGANIC EXTRACT OF SOIL
(WEYAND, *et al*., 1996)

Diet	[a]Pyrene Ingested (µg/mouse)	[b]Pyrene Excreted (µg/mouse)	[c]Fractional Urinary Excretion
Extracted Soil #1	0	0	ND
Extracted Soil #2	0	0	ND
Soil #1	0.60	0.039	6.2
Soil #2	30.42	0.527	1.7
Organic Extract #1	0.56	0.097	17.2
Organic Extract #2	25.91	4.16	16.1

[a]The sum of 1-OH P-GlcUA, 1-OH P-Sul, and 1-OH P levels is expressed in terms of equivalents of pyrene.
[b]The amount of soil and pyrene consumed in metabolism cages on day 15 over a period of 24 hr.
[c]Fractional Urinary Excretion = (amount of pyrene excreted / amount of pyrene consumed on day 15) x 100. (The authors termed this "bioavailability." Because this is a nonstandard use of the term, it is renamed here.)

Note: Soil #1: 1 ppm pyrene; 9 ppm total PAHs; Soil #2: 35 ppm pyrene; 377 ppm total PAHs.

The RAF from soil #2 was 11% (1.7%/16.1% x 100). This study clearly shows that pyrene in aged soil is absorbed in the gastrointestinal tract to a lesser degree than is pyrene added to rodent food as an organic extract.

DNA adducts in lung tissue were also measured for soil #2 (246 cPAH) and its organic extract, and the resulting RAF, which is relevant to potentially carcinogenic PAHs, is 0.17.

Koganti, et al. (1998)

Koganti, *et al*. (1998), is another study by workers in Weyand's laboratory and the methods described above were also used here. In this case, soils and soil extracts from three MGP sites were fed to female mice. However, in contrast to earlier work from this laboratory, two measurements of systemic absorption of PAH were used. The first method was equivalent to that described for earlier studies: measurement of urinary metabolites of pyrene. The second method was the quantitative measurement of covalent binding of PAH metabolites to DNA of lung tissue (DNA adducts). This is of interest because the measurements may address the absorption of two different groups of PAH. Pyrene is a low molecular weight PAH with less affinity for soil sorption than higher molecular weight PAH, such as B(a)P. Thus, the pyrene metabolite measurements may relate specifically to low molecular weight PAH and might be hypothesized to be more available for absorption from a soil matrix than higher molecular weight compounds. DNA adduct measurement may be indicative of the absorption of high molecular weight PAH and may be used to evaluate comparative absorption of high molecular weight PAH, if combined with the appropriate measure of PAH dosing.

Koganti, *et al* (1998) fed mice (four in each dosing group) with a mixture of soil and feed or organic extract or soil plus feed at three to four different nominal concentrations. RAFs were calculated based on the ratio of fractional urinary excretion (described in the discussion of the Weyand, 1996 report) observed between animals fed soils and those fed organic extract of the soil. The results of this evaluation are shown in Table 4 of Koganti, *et al*. (1998). Although Koganti, *et al*. (1996) used a soil or extract addition to make up several different final concentrations of PAH in the feed, no trend in fractional absorption with concentration was observed. Therefore, all RAFs calculated in this report were used separately and are included in the RAF summary table for pyrene metabolites of this report (Table 7).

In addition to measurement of pyrene metabolites in urine, Koganti, *et al*. (1998) quantified DNA adducts. Adducts were measured in only one large organ (lung) and do not fully capture total adduct mass in the animal. However, Koganti, *et al*. (1998) used a ratio approach to calculate the "fractional lung adduct" as a proportion of the total exposure to PAH (mg PAH per mouse). The ratio of fractional lung adduct in mice fed to that observed in mice fed organic extract is a means of calculating RAFs that is identical to the fractional urinary excretion method described above. Koganti, *et al*. (1998) expressed the opinion that only higher molecular weight PAH generally believed to be rodent or human carcinogens were responsible for DNA adduct formation. Therefore, they normalized fractional lung adducts based on the total exposure of each mouse to "carcinogenic PAH" (cPAH). As such, the RAFs calculated from DNA adduct quantification (these appear in Table 5 of Koganti, *et al*. (1998)) may be specifically relevant to high molecular weight, potentially carcinogenic PAH. These RAFs are summarized in a separate table in this report, along with other RAFs that may also be specifically relevant to cPAH (Table 8). As with previously-described observations using

pyrene metabolites, Koganti, *et al*. (1998) discern no association of RAF with the concentration of cPAH administered, so Table 8 contains all RAF calculations.

Goon, et al. (1991)

Goon, *et al.* (1991) studied the bioavailability of a specific PAH, benzo(a)pyrene, administered orally as the pure chemical or as B(a)P adsorbed onto soil particles. Additional information about the study was obtained directly from the authors (Goon, *et al*., 1996) and an analysis of the work of Goon and co-workers has been published (Magee, *et al*, 1996)Male Sprague-Dawley rats were gavaged with B(a)P mixed with ^{14}C-B(a)P in solution [0.5% Tween 80 (v/v in saline)] (1.0 µmol B(a)P/kg, 25 µCi/kg) or the equivalent dose adsorbed onto a clay-based soil or a sand-based soil. The soils consisted of 2.5 g solid/kg containing 100 mg/kg B(a)P. All animals received 7.5 mL of 0.5% Tween 80 (v/v in saline).

Venous blood samples were collected from the retro-orbital plexus at predetermined times (0.5, 1, 2, 4, 8, 12, 24, 48, 72, 96, 120, 144, and 168 hours), and excreta were collected continuously over 24-hour intervals. After 168 hours, animals were euthanized and tissues collected for analysis. Total radioactivity was measured by liquid scintillation in blood, urine, feces, and tissues.

The sandy soil was classified as a loam which was very low in organic content, 0.04%. It contained 47% sand, 41% silt, and 12% clay. The pH was 6.5, and the cation exchange content was 0.6 meq/100 g. The clay-based soil was classified as clay with low organic content, 1.35%. It contained 6% sand, 18% silt, and 76% clay. The pH was 7.0 and the cation exchange content was 45.65 meq/100 g. The sandy soil was ground and sonic sifted. The clay-based soil was dried and passed through a Brickman ultra-centrifugal mill. In both cases, the particles size was small, <100 um. Both soils were washed twice with methylene chloride and dried before use. This destroyed any microbial activity that may have existed in the soils.

B(a)P and ^{14}C-B(a)P were added in acetone to soils. The acetone was evaporated, leaving soils that were 100 ppm in B(a)P and 10 uCi/g in radiolabel. Animals were administered the soil-adsorbed B(a)P at various time intervals after the soil and the B(a)P were mixed: 1 day, 7 days, 30 days, 6 months and one year. Animals were fasted for 12 hours prior to dosing. Two hours after dosing, Purina Rodent Chow 5001 and water were available *ad libitum*.

In this experiment, three dosing vehicles were prepared that contained radiolabeled B[a]P: emulsified aqueous solution, sandy soil, and clayey soil. Male Sprague Dawley rats were gavaged with the three vehicles and followed for seven days. Blood, urine, and feces were measured at numerous time points for seven days. After seven days, the animals were sacrificed, and more than ten tissues were analyzed for radiolabel. Animals received equal doses of B[a]P regardless of dosing group.

After the initial experiment, the same vehicles were administered to different animals after seven days, one month, six months, and one year. Recoveries for these experiments were reasonable:

Solution:	76%
Sandy Soil:	102%
Clayey Soil:	105%

After normalizing to each animal's individual total recovery, the data were summarized and RAFs were derived by comparing the fractional seven-day urinary excretion to that in the solution group and by comparing the seven day blood area-under-the-curve to that in the solution group (see Table 4). Because the reanalysis of the 1990 experiment showed that there was no difference between the solution and diet groups, no normalization of the results of the solution groups was deemed necessary to create RAFs that are directly relevant to use with the cancer slope factor, which was derived from dietary studies.

TABLE 4
SUMMARY OF RAFS FROM GOON, *et al*. (1991) REANALYSIS

	Urinary RAF	**Urinary RAF**	**Blood AUC RAF**	**Blood AUC RAF**
Ageing Period	**Sandy Soil**	**Clayey Soil**	**Sandy Soil**	**Clayey Soil**
One Day	0.47	0.40	0.43	0.35
Seven Days	0.46	0.52	0.49	0.38
One Month	0.56	0.40	0.45	0.36
Six Months	0.48	0.33	0.37	0.22
One Year	0.50	0.26	0.40	0.24

For site aged sandy soil the RAF based on the blood AUC data is 0.39. The RAF based on urinary data is 0.49. These values are the averages of the six month and one year experiments.

For site aged clayey soil the RAF based on the blood AUC data is 0.23. The RAF based on urinary data is 0.30. These values are the averages of the six month and one year experiments.

One way to measure relative bioavailability is to compare the area under the blood curve (AUC) for total radiolabel over the entire 168 hour experimental period during which blood B(a)P levels were measured. Radiolabel in the blood represents a fraction the

B(a)P that was absorbed in the gastrointestinal tract, including parent B(a)P and metabolites.

The use of AUC measurements is a classic approach in drug pharmacology where systemic bioavailability is defined as the blood AUC after an intravenous dose divided by the AUC after an oral dose. In the case of drugs, the amount of parent drug circulating in the blood over a long period of time is of primary interest, because, in most cases, first pass metabolism of the drug in the liver reduces the drug efficacy. Metabolites are inactive and are excreted. Thus, total blood levels of parent drug are of greater interest than are the levels of drug plus metabolites.

This same concern is not relevant for the risk assessment of PAHs, such as B(a)P, because B(a)P is not direct acting. No toxic effects are manifested by the parent, unmetabolized B(a)P. Instead, metabolism is required for toxicity. It is the metabolites of B(a)P and other PAH that bind to cellular macromolecules, such as DNA, and cause adverse effects in various tissues. Metabolism of PAHs occurs in all tissues, and orally administered B(a)P has caused tumors in laboratory animals in various tissues, including stomach, lung, esophagus, larynx, and others. B(a)P metabolism is also multi-stepped. In order for the B(a)P diol epoxide, the putative mutagenic metabolite, to be formed, several metabolic conversions involving several enzymes must occur.

Thus, in some cases the toxic metabolite in a distant tissue, such as the lung, is caused by a B(a)P molecule that was absorbed through the gastrointestinal tract, was *not* metabolized in the liver, circulated through the blood, and was metabolized in several steps in the lung. In other cases, the toxic lung metabolite was formed by a molecule that was absorbed though the gastrointestinal tract, was metabolized to an intermediate metabolite in the liver, and circulated through the blood as a B(a)P metabolite, and was metabolized several more times in the lung to a toxic metabolite.

In addition, B(a)P and B(a)P metabolites excreted in the bile are known to be reabsorbed in the gastrointestinal tract by a process known as enterohepatic recirculation (Chipman, *et al*., 1981). Thus, some B(a)P metabolites are known to be excreted into the bile and the gastrointestinal tract. When present in the gastrointestinal tract parent B(a)P can be reabsorbed. In addition, conjugated metabolites, such as glucuronide, sulfate, and glutathione metabolites can be de-conjugated by enzymes residing in bacteria present naturally in the gastrointestinal tract. After de-conjugation, the primary metabolite can and is reabsorbed. After reabsorption, it can travel to a distant tissue via the systemic circulation and cause damage.

Thus, for B(a)P and other PAHs, the circulating blood level of just the parent compound is not a relevant dose metric. Instead, the total B(a)P dose including parent B(a)P and metabolites is the critical parameter to measure. This is because some metabolites are directly toxic to distant tissues, some metabolites are metabolic precursors of secondary metabolites that are toxic to distant tissues and can be formed therein, and some metabolites can be excreted and reabsorbed and can later cause damage in distant tissues, including the gastrointestinal tract itself.

While the total blood radiolabel AUC from 0-168 hours does not define the fraction of the administered B(a)P that was absorbed in an animal or a treatment group, the ratio of AUC measurements for two treatment groups administered the B(a)P by the same route

of exposure in an excellent measure of *relative* bioavailability between the two treatment groups.

AMEC notes that the two soils studied were very low in organic content (0.04% and 1.35%). Certainly, the value for sandy soil is much lower than a typical soil. For instance, in its Risk Based Corrective Action guidance, the ATSM assumes 1% as a default value for typical soils. Accordingly, the RAF for clay-based soil is probably more typical of average soils than the RAF for sandy soil.

Goon, et al. (1990)

In an earlier experiment, Goon, *et al*. (1990) studied the bioavailability of B(a)P in aqueous solution, in laboratory chow, in unaged sandy soil and in unaged clay-based soil. Additional information was obtained directly from the authors (Goon, *et al*., 1996). The study was performed in the same manner as the one described above with the exception that 4 male rats and 4 female rats were placed in each of four study groups, including rodent chow.

AMEC rejected the data from the Goon, *et al*. (1990) study for RAF derivation and relied solely on the 1991 experiment because of low recovery and high variability.

After dosing, urine, feces, and blood were analyzed for seven days. Then, at the end of seven days, the animals were sacrificed, and all tissues were analyzed. Total recovery of B[a]P was calculated by comparing the amount recovered to the amount administered. Recoveries of total B[a]P were generally poor in all treatment groups in the 1990 study:

Solution	75%
Diet	62%
Sand	65%
Clay	48%

It is not known what the cause of the poor recoveries was, but such poor recovery of administered dose is reason enough to reject this study from RAF derivation.

However, for the sake of completeness AMEC summarized the tissue, urine, and fecal B[a]P for each animal. In view of the high variability among animals within treatment groups, each animal was analyzed separately, and statistical tests were performed to determine if the groups were statistically significantly different from each other. Because only total radiolabel was measured, one cannot distinguish between unmetabolized B[a]P and B[a]P metabolites in the feces. Tissue radioactivity was found to be insignificant compared to the amount excreted in the urine. Thus, it is not possible to make estimates of total absorption from this experiment. Accordingly, relative bioavailability is determined by comparing the amount of the administered dose cumulatively found in the urine over the seven day period after dosing.

TABLE 5
SUMMARY OF URINARY EXCRETION RESULTS
GOON, *et al*. (1990)

TREATMENT GROUP	MEAN FRACTIONAL 7-DAY URINARY EXCRETION (%)*	STANDARD DEVIATION (%)	SAMPLE SIZE
Solution	4.9 % (1)	1.9 %	8
Diet (unaged)	4.4 % (2)	1.8 %	10
Solution + Diet (unaged)	4.6 % (3)	1.8 %	18
Sand (unaged)	3.7 % (4)	2.2 %	10
Clay (unaged)	1.9 % (5)	0.8 %	8

* Total amount detected in urine over seven days (nmol) / administered dose (nmol) x 100.
(1) Not significantly different from diet group.
(2) Not significantly different from solution group.
(3) Solution and diet groups combined.
(4) Not significantly different from solution + diet group.
(5) Significantly different from solution + diet group.

As noted above (see Table 5), bioavailability as measured by urinary excretion was not statistically different between the solution and diet groups. This finding differs from the results reported by Goon, *et al*. (1990) for two reasons. First, the urinary, fecal and tissue data had not been analyzed at that time, and estimates of urinary excretion were lacking. Second, the blood area-under-the-curve (AUC) data presented by Goon, *et al*. in 1990 were grouped, so that the great variability from animal-to-animal was masked. The result that follows the animal-by-animal reanalysis of the raw data is consistent with the general literature on PAH absorption.

Because the solution and diet groups were not different, data from these two groups were merged for comparison with the sand and clay groups. Bioavailability was not statistically different between the solution/diet group and the unaged sand group. This contradicts results from the study that were presented at the 1990 Society of Toxicology meeting, which indicated that the bioavailability from the sand group was *higher* than from the solution and diet groups. In fact, the mean urinary excretion in the sand group is lower than the absorption in the solution, diet, or diet/solution group. Because of the great variability within both groups, however, there is no statistically significant difference between the solution/diet and sand groups. This result does not demonstrate that the presence of sandy soil has no effect on bioavailability. Instead, the experiment has so much variability in it that the experiment is unable to detect any difference that may actually exist.

Bioavailability as measured by cumulative urinary excretion *was statistically different* between the solution/diet group and the unaged clay group. This confirms results from the study that were presented at the 1990 Society of Toxicology meeting, which indicated a lower bioavailability from the clay group. Results could be used to derive an RAF for unaged clay (RAF=0.42).

In conclusion, the animal-by-animal evaluation of the data from the Goon, *et al*. (1990) study shows there is very high animal-to-animal variability and that recoveries of administered B[a]P were low, ranging from 48% to 75%. Because of the high variability, statistical tests show that there is no difference in the bioavailability of B[a]P in the groups treated with the test chemical in emulsified aqueous solutions, dietary vehicle, or in sandy soil. There was a statistically significant difference in the B[a]P absorption from clayey soil. We conclude from this detailed analysis that the experiment in which males and female animals were both used lacks sufficient power to measure bioavailability and must be rejected for RAF derivation purposes.

Magee, et al. (1999)

Magee, *et al*. (1999) studied the absorption of PAH from soils collected from residential yards in the vicinity of a Superfund site (not MGP waste). Three samples (identified as 007-009) were selected from available material based on the availability of a size fraction (<250 μm) most appropriate for absorption studies. The concentration of PAH in the soils ranged from 66 to 388 ppm, and benzo[a]pyrene- toxic equivalent concentrations range from 9 to 70 ppm.

This study was performed using organic extracts of the soils as an internal control, as was described in the discussion of studies by Weyand, *et al*. (1996). Powder rat chow containing either soil or organic extract of that soil was fed to mice (2 replicates of 4 mice each for each of the 3 soil samples) for 14 days and urine was collected for analysis of both pyrene and B(a)P metabolites. Additionally, rats were sacrificed at the end of the exposure period and lung tissue was harvested for quantification of DNA adducts. RAFs were calculated as the ratio of either the fractional urinary excretion of B(a)P metabolites or the fractional lung adducts between soil and organic extract fed mice (the lung adducts were divided by cPAH exposure, as done in the Koganti, *et al*. (1998) study and therefore relates specifically to cPAH availability). The average fractional urinary excretion and fractional lung adduct values for each soil sample (based on observations in eight animals each) are shown in Table 6, with the corresponding RAF.

TABLE 6
RAF CALCULATIONS OF B(A)P AND cPAH RAFS
MAGEE, *et al*. (1999)

Soil Sample	Mean Fractional Urinary Excretion of 3-hydroxy B(a)P (ug 3OH-B(a)P per mouse/ug BaP ingested per mouse)		RAF based on B(a)P metabolite excretion	Mean Fractional Lund Adduct (pmol/mg DNA per mouse/mg cPAH ingested per mouse)		RAF based on DNA Adducts
	Soil	Organic Extract		Soil	Organic Extract	
Soil 009	0.0116	0.1587	0.07	3.04	40.99	0.07
Soil 008	0.0375	0.386	0.1	6.97	36.14	0.19
Soil 007	0.0587	0.2029	0.29	5.93	16.31	0.36

Bordelon, et al. (2000)

Bordelon, *et al*. (2000) studied the oral bioavailability of coal tar from soil in Fischer 344 male rats. The soil contained 0.35% coal tar, and had been aged for 9 months. DNA adduct levels (normalized to moles of normal nucleotides, quantity of PAH ingested, and body weight) were determined in liver and lung.

Relative bioavailability of coal tar from soil was calculated as the ratio of relative DNA adduct levels (per mg PAH ingested per kg body weight) in rats receiving 0.35% coal tar in aged soil, to relative DNA adduct levels (per mg PAH ingested per kg body weight) in rats receiving 0.35% coal tar directly. Relative coal tar bioavailabilities, based on hepatic and lung DNA adduct levels, were 0.35 and 0.44, respectively.

Grøn, et al. (2007)

Grøn, *et al*. (2007) studied the oral bioavailability of benzo(a)pyrene and dibenz(a,h)anthracene from four Danish soils (identified as 4, 5, 6, and 7) in minipigs. Three of the soils were contaminated with mine waste and one was contaminated with household and construction waste. The concentrations of B(a)P and Db(a,h)A in Soil 4 were 6.0 and 0.77 mg/kg dry weight, respectively. The concentrations of B(a)P and Db(a,h)A in Soil 5 were 270 and 43 mg/kg dry weight, respectively. The concentrations of B(a)P and Db(a,h)A in Soil 6 were 70 and 19 mg/kg dry weight, respectively. The concentrations of B(a)P and Db(a,h)A in Soil 7 were 22 and 5.4 mg/kg dry weight, respectively.

Relative bioavailability of B(a)P from each soil sample was calculated as the ratio of the absolute soil B(a)P bioavailability to the absolute B(a)P bioavailability from a hexane solution. Absolute bioavailability was determined as the fraction of ingested B(a)P not excreted with feces. Relative bioavailability of B(a)P from Soils 4, 5, 6, and 7, was determined to be 0.36, 0.55, 0.48, and 0.47, respectively.

Relative bioavailability of Db(a,h)A from each soil sample was calculated as the ratio of the absolute soil Db(a,h)A bioavailability to the absolute B(a)P bioavailability from a hexane solution (the absolute bioavailability of Db(a,h)A for hexane solution was not determined). Absolute bioavailability was determined as the fraction of ingested Db(a,h)A not excreted with feces. Relative bioavailability of Db(a,h)A from Soil 4 was not determined. Relative bioavailability of Db(a,h)A from Soils 5, 6, and 7, were determined to be 0.30, 0.28, and 0.27, respectively.

RAF Derivation

Several estimates of oral-soil RAFs were derived from six studies, as shown in Tables 7 and 8. These estimates of oral-soil RAFs were derived from studies with B(a)P, a five-ring potentially carcinogenic PAH, and Db(a,h)A, a 5-ring PAH for a general measure of cPAH; and pyrene, a four-ring noncarcinogenic PAH for a general measure for ncPAH. Because of the physical property differences (specifically, affinity for sorption to soil) between low molecular weight PAH such as pyrene and the higher molecular weight PAH such as B(a)P and other cPAH, it is likely that the relative absorption of these subclasses of PAH will be different. Indeed, the mean and 90th percentile RAFs based on pyrene (Table 7) are 0.45 and 0.78, respectively (calculated from the full distribution of results using @RISK® software and assuming data are normal), whereas the mean and 90th percentile RAFs based on B(a)P and other cPAH are smaller: 0.25 and 0.53, respectively (calculated from the full distribution of results using @RISK® software and assuming data are exponential). It is recommended that the 90th percentile pyrene RAF be used for all low molecular weight PAH and the 90th percentile value of observations from Table 8 be used for all cPAH.

TABLE 7
SUMMARY OF ORAL-SOIL RAFS FOR PYRENE

Oral-Soil RAF	Notes	Source
0.08	B6CF1 mice, Site B MGP soil, 1 ppm pyrene, 4 ppm tPAH	Koganti, *et al.* (1998)
0.11	B6CF1 mice, Site B MGP soil, 5 ppm pyrene, 36 ppm	Koganti, *et al.* (1998)
0.11	B6C3F1 mice, MGP soil, 35 ppm pyrene, 377 ppm tPAH	Weyand, *et al.* (1996)
0.21	B6C3F1 mice, Site A MGP soil, 17 ppm pyrene, 135 ppm tPAH	Koganti, *et al.* (1998)
0.26	B6CF1 mice, Site C MGP soil, 627 ppm pyrene, 3120 ppm tPAH	Koganti, *et al.* (1998)
0.30	B6CF1 mice, Site A MGP soil, 193 ppm pyrene, 1600 ppm tPAH	Koganti, *et al.* (1998)
0.31	B6CF1 mice, Site B MGP soil, 148 ppm pyrene, 975 ppm tPAH	Koganti, *et al.* (1998)
0.36	$B_6C_3F_1$ mice, MGP soil, 1 ppm pyrene, 9 ppm tPAH	Weyand, *et al.* (1996)
0.46	$B_6C_3F_1$ mice, MGP soil, 57 ppm pyrene, 456 ppm tPAH	Magee, *et al.* (1998)
0.47	$B_6C_3F_1$ mice, MGP soil, 44 ppm pyrene, 388 ppm tPAH	Magee, *et al.* (1998)
0.52	B6CF1 mice, Site C MGP soil, 3 ppm pyrene, 20 ppm tPAH	Koganti, *et al.* (1998)
0.55	B6CF1 mice, Site A MGP soil, 1 ppm pyrene, 8 ppm tPAH	Koganti, *et al.* (1998)
0.75	B6CF1 mice, Site A MGP soil, 0.2 ppm pyrene, 0.6 ppm	Koganti, *et al.* (1998)
0.97	$B_6C_3F_1$ mice, MGP soil, 7 ppm pyrene, 66 ppm tPAH	Magee, *et al.* (1998)
1.0	B6CF1 mice, Site C MGP soil, 21 ppm pyrene, 132 ppm tPAH	Koganti, *et al.* (1998)

TABLE 8
SUMMARY OF ORAL-SOIL RAFS FOR B(A)P AND cPAH

Oral-Soil RAF	Notes	Source
0.07	B6C3F1 mice MGP soil; 48 ppm BAP, 388 ppm tPAH (BAP metabolites)	Magee, *et al.* (1998)
0.07	B6C3F1 mice MGP soil; 239 ppm cPAH, 388 ppm tPAH (DNA adducts)	Magee, *et al.* (1998)
0.08	B6C3F1 mice, Site A MGP soil, 86 ppm cPAH, 135 ppm tPAH (DNA adducts)	Koganti, *et al.* (1998)
0.10	B6C3F1 mice MGP soil; 50 ppm BAP, 456 ppm tPAH (BAP metabolites)	Magee, *et al.* (1998)
0.15	B6C3F1 mice, Site B MGP soil, 24 ppm cPAH, 36 ppm tPAH (DNA adducts)	Koganti, *et al.* (1998)
0.17	B6C3F1 mice, Site A MGP soil, 5 ppm cPAH, 8 ppm tPAH (DNA adducts)	Koganti, *et al.* (1998)
0.17	B6C3F1 mice, MGP soil, 247 ppm cPAH, 377 ppm tPAH (DNA adducts)	Weyand, *et al.* (1996)
0.20	B6C3F1 mice, Site C MGP soil, 895 ppm cPAH, 3120 ppm tPAH (DNA adducts)	Koganti, *et al.* (1998)
0.19	B6C3F1 mice MGP soil; 271 ppm cPAH, 456 ppm tPAH (DNA adducts)	Magee, *et al.* (1998)
0.23	Sprague-Dawley Rats, clay-based soils, 100 ppm BAP, 100 ppm tPAH (blood measurements)	Goon, *et al.* (1991)
0.27	Minipigs; Danish contaminated soil 7; 5.4 mg/kg dw DiB(ah)anth; fraction of ingested PAH not excreted in feces.	Gron, *et al.* (2007)
0.28	Minipigs; Danish contaminated soil 6; 19 mg/kg dw DiB(ah)anth; fraction of ingested PAH not excreted in feces.	Gron, *et al.* (2007)
0.29	B6C3F1 mice MGP soil; 6 ppm BAP, 66 ppm tPAH (BAP metabolites)	Magee, *et al.* (1998)
0.30	Sprague-Dawley Rats, clay-based soils, 100 ppm BAP, 100 ppm tPAH (urine measurements)	Goon, *et al.* (1991)

0.30	Minipigs; Danish contaminated soil 5; 43 mg/kg dw DiB(ah)anth; fraction of ingested PAH not excreted in feces.	Gron, *et al.* (2007)
0.32	B6C3F1 mice, Site B MGP soil, 238 ppm cPAH, 975 ppm tPAH (DNA adducts)	Koganti, *et al.* (1998)
0.35	Fischer 344 rats; soil aged for 9 months with 0.35% coal tar; DNA adducts in liver.	Bordelon, *et al.* (2000)
0.36	B6C3F1 mice MGP soil; 41ppm cPAH, 66 ppm tPAH (DNA adducts)	Magee, *et al.* (1998)
0.36	Minipigs; Danish contaminated soil 4; 6.0 mg/kg dw BaP; fraction of ingested PAH not excreted in feces.	Gron, *et al.* (2007)
0.39	Sprague-Dawley Rats, sandy soils, 100 ppm BAP, 100 ppm tPAH (blood measurements)	Goon, *et al.* (1991)
0.44	Fischer 344 rats; soil aged for 9 months with 0.35% coal tar; DNA adducts in lung.	Bordelon, *et al.* (2000)
0.47	B6C3F1 mice, Site A MGP soil, 986 ppm cPAH, 1600 ppm tPAH (DNA adducts)	Koganti, *et al.* (1998)
0.47	Minipigs; Danish contaminated soil 7; 22 mg/kg dw BaP; fraction of ingested PAH not excreted in feces.	Gron, *et al.* (2007)
0.48	Minipigs; Danish contaminated soil 6; 70 mg/kg dw BaP; fraction of ingested PAH not excreted in feces.	Gron, *et al.* (2007)
0.49	Sprague-Dawley Rats, sandy soils, 100 ppm BAP, 100 ppm tPAH (urine measurements)	Goon, *et al.* (1991)
0.55	Minipigs; Danish contaminated soil 5; 270 mg/kg dw BaP; fraction of ingested PAH not excreted in feces.	Gron, *et al.* (2007)
0.76	B6C3F1 mice, Site C MGP soil, 55 ppm cPAH, 132 ppm tPAH (DNA adducts)	Koganti, *et al.* (1998)

3.3 RAF for Dermal Exposure to Soil

Two studies were identified in which the dermal absorption of PAHs was measured from a soil matrix. These include Yang, *et al.* (1989) and Wester, *et al.* (1990). These studies are discussed below. Estimates of dermal-soil RAFs can be derived from the results of these studies when combined with data on absorption from investigations using dosing methods similar to the dose-response studies.

Studies

Yang, et al. (1989)

Yang, *et al*. (1989) measured the percutaneous absorption of benzo(a)pyrene (B(a)P) from petroleum crude-fortified soil and from pure petroleum crude oil both in live rats and in *in vitro* studies using excised rat skin (see Table 9). The soil was a loam containing 1.64% organic matter, 46% sand, 36% silt, and 18% clay. The B(a)P-soil mixture was prepared by adding the radiolabelled crude oil in dichloromethane to the soil. The solvent was removed by rotary evaporator. All soils were used within 72 hours of preparation.

Radiolabelled B(a)P (^{3}H-B(a)P) was added at a known concentration for quantification. In the *in vivo* experiments, soil containing B(a)P in crude petroleum or pure crude petroleum containing B(a)P was applied to the dorsal skin of the female Sprague-Dawley rats. In both cases, the dose of B(a)P was 0.01 ug/cm^2. For the crude oil, 90 ug/cm^2 of oil containing 100 ppm B(a)P was applied. For soil, 9 mg/cm^2 of soil containing 1 ppm of B(a)P was applied. The dorsal area was covered with a non-occlusive glass cell to prevent ingestion of the B(a)P by grooming behavior.

Absorption was determined by measuring the radioactivity in the urine and feces once daily and the urine, feces and tissues at 96 hours. Data from five animals were averaged. After 96 hours, cumulative absorption of B(a)P from crude-soaked soil (9.2%) was less than that from the crude alone (35.3%).

In the *in vitro* experiments, dorsal skin was excised from female Sprague-Dawley rats after sacrifice. 350 um skin sections were placed in consoles containing 15 mm diameter Franz diffusion cells. The receptor fluid was an aqueous solution of 6% Volpo-20, a nonionic surfactant. The absorption was measured by analyzing the surfactant containing receptor fluid that bathed the receiving reservoir of the absorption chamber for radiolabelled B(a)P. The receptor fluid was sampled once every 24 hours for four days. Data from five trials were averaged. Again, 96 hour cumulative absorption was greater for B(a)P in oil (38.1%) versus B(a)P in oil-soaked soil (8.4%).

TABLE 9
DERMAL ABSORPTION OF BENZO(a)PYRENE FROM SOIL IN THE RAT
YANG, *et al*. (1989)

Time Point	*In Vivo* Results	*In Vitro* Results
24 Hours[1]	1.1% (0.3)[1,2]	1.5%[4]
48 Hours[1]	3.7% (0.8)[1,2]	3.5%[4]
72 Hours[1]	5.8% (1.0)[1,2]	5.5%[4]
96 Hours[3]	9.2% (1.2)[1,3]	8.4%[4]

[1]Values shown for 48-96 hours are cumulative. Results are the mean for five rats (standard error).
[2] Urine plus feces
[3] Urine plus feces plus tissues.
[4] See Figure 1 of Yang, *et al.* (1989)

Wester, et al. (1990)

Wester, *et al*. (1990) measured the absorption of B(a)P *in vivo* over 24 hours in the monkey using acetone as vehicle or using soil containing B(a)P at the 10 ppm level (see Table 10). The soil used contained 26% sand, 26% clay, and 48% silt. The organic content was not specified. The B(a)P containing soil was prepared by adding the B(a)P in (7:3, v/v) hexane:methylene chloride. The soil was mixed by hand and left open to the air to allow dissipation of the solvent. The B(a)P-soil mixture was not aged before use.

Four female Rhesus monkeys were tested with 40 mg soil/cm^2 applied to the abdominal skin. The skin area was covered with a nonocculusive cover to prevent loss of soil or ingestion of soil by grooming behavior. Percutaneous absorption was measured by comparing the quantity of radiolabel (^{14}C-B(a)P) in the urine following topical application to that following intravenous application. Urine was collected for 24 hours. After 24 hours, all visible soil was collected from the application site. The skin surface was washed with soap and water, and the monkeys were returned to metabolic cages for urine collection for an additional six days. *In vivo*, the absorption was 51.0% for acetone vehicle and 13.2% for soil.

In vitro studies were also carried out with viable human cadaver skin in cells of the flow-through design. Human serum was used as the receptor fluid. Radiolabel was determined in the receptor fluid after 24 hours as well as in the skin after a surface wash with soap and water. The amount of B(a)P that cannot be removed from the skin with a soap and water wash is designated here as "absorbed" for the purposes of RAF derivation. In six experiments with skin from two donors, 23.8% of the B(a)P was absorbed with acetone vehicle. From soil (10 ppm), 1.45% was absorbed in 24 hours.
Roy, et al (1998)

This investigation is worth mention because it utilized soils from sites containing MGP tars. And is the most recent evaluation of dermal absorption. In this paper, the authors

note substantial reduction in the absorption of B(a)P in soils applied to skin in an in vitro diffusion apparatus when compared to organic extracts of the same material. However, these investigators used an excess of B(a)P source in doing these experiments and, as such, are calculating the flux rate of B(a)P under conditions of “infinite source”. Thus, while the absorption reduction is interesting, it cannot be converted to an RAF for risk assessment purposes in that both the dose-response data and the relevant environmental exposure (dermal absorption of PAH on the skin) are likely to be finite sources, that are controlled as much by reduction in avialable PAH as the rate at which the compounds cross the skin. Therefore, this study was not used to estimate RAFs for the dermal absorption exposure route.

RAF Derivation

The fraction absorbed in a 24-hour or 96-hour experiment has little relevance to human risk assessment. Receptors who might touch, walk on, or otherwise contact PAH-containing soil would only realistically be exposed for a period of 6-12 hours at maximum before washing themselves or before the soil would drop off or be rubbed off the skin. The Wester, *et al*. (1990) paper demonstrates that soap and water wash can remove a large amount of the administered dose (53-91%), even after 24 hours. Even more would be removed after only 6-12 hours exposure.

U.S. EPA guidance for dermal risk assessment recognizes that the time period of a dermal experiment is an important factor to consider when evaluating experimental data. U.S. EPA (1992b) has noted: "The experiment should provide absorption estimates over a time corresponding to the time that soil is likely to remain on skin during actual human exposures."

TABLE 10
DERMAL ABSORPTION OF BENZO(a)PYRENE FROM SOIL
WESTER, *et al*. (1990)

Sample	Monkey Skin	Human Skin
1	13.1%[1]	1.01%[3]
2	10.8%[1]	1.52%[3]
3	18.0%[1]	0.61%[3]
4	11.0%[1]	2.21%[3]
5	NA	0.31%[3]
6	NA	3.01%[3]
Mean +/- SD	13.2% +/- 3.4%[2]	1.45% +/- 1.02% [2]

[1]Percentage of applied dose absorbed = (^{14}C urinary excretion for seven days following 24 hour topical application) /(^{14}C urinary excretion following intravenous administration) x 100
[2] Mean +/- Standard Deviation
[3] Fraction of applied dose in the skin plus fraction in receptor fluid.

Accordingly, the data from the Yang, *et al.* (1989) and Wester, *et al.* (1990) experiments should be prorated for a reasonable exposure period, such as 6-12 hours. A health-protective way to do this is to simply assume that absorption is linear over time. The Yang, *et al*. (1989) *in vitro* study showed a linear absorption into rat skin from 24-96 hours, but no data are available for the 0-24 hour period.

In fact, Kao, *et al*. (1985) have shown that the appearance of radiolabel from topically applied benzo(a)pyrene and other chemicals in human, rodent, and other species' skin in the culture medium of their *in vitro* system was exponential, not linear. A distinct time lag is apparent before any absorption occurs. A time lag has also been shown for various chlorophenols in human skin (Roberts, *et al*., 1977; Huq, *et al*., 1986). U.S. EPA (1992b) also recognizes that a time lag may exist: "time is required after initial contact with the skin for such a steady-state to be achieved." Also: "Linear adjustments may not be accurate, since it is unknown how soon steady-state is established and since steady-state conditions may not be maintained throughout the experiment due to mass balance constraints."

Thus, linear adjustments of 24 hour absorption data to estimate absorption over 6-12 hours may overestimate the true absorption, but it is not likely to underestimate absorption. A health-protective approach would be to assume that a relevant absorption period is as high as 8 hours. (U.S. EPA in its recently proposed Hazardous Waste Identification Rule assumes 8 hour exposures.) With this assumption, the Yang, *et al.* (1989) data from the *in vitro* experiment can be adjusted to 0.27% absorption over 8 hours using a linear regression of all four time points. The data from the *in vivo* experiment can be adjusted to 0.8% absorption over 8 hours. The 96 hour data is used in this case, because tissue-bound B(a)P was measured only for this time point. The 8

hour estimated absorption using a linear regression is only 0.01%, and was thus rejected for RAF derivation.

The Wester, *et al*. (1990) data can be adjusted to 4.4% absorption in the *in vivo* monkey experiment over an 8 hour exposure period. Similarly, the 8 hour estimated exposure for the *in vitro* human skin experiment is 0.48%.

For deterministic risk assessments, single estimates of dermal-soil RAFs are needed both for potentially carcinogenic PAHs and for non-carcinogenic PAHs.

Four estimates of the dermal absorption of PAHs from soil were presented: 0.27%, 0.80%, 4.4%, and 0.48%. In addition, 12 estimates of the absorption of PAHs from the dose-response study were presented in Table 1. The average value is 92%. Four RAF estimates are 0.003, 0.009, 0.048, and 0.005. These four RAFs are used to develop the distribution of dermal RAFs for PAHs. The deterministic estimate of the dermal-soil RAF for potentially carcinogenic PAHs is simply the 90th percentile of the four RAFs, 0.03 (calculated from the full distribution of results using @RISK® software and assuming data are normal).

Applicability to Potentially Carcinogenic PAHs

Dermal-soil RAFs have been derived for B(a)P based on four experimental data points with B(a)P. However, risk assessment of PAHs involves the calculation of benzo(a)pyrene-toxic equivalents, which includes the seven PAHs designated as potentially carcinogenic. The following section addresses the applicability of the B(a)P RAF to other potentially carcinogenic PAHs.

Various researchers have investigated the dermal absorption of different PAHs from pure mixtures, such as coal tar, or from solvent vehicles, such as acetone. From these studies, data on the comparative dermal absorption of various pure PAHs are available, but no studies are available on the dermal absorption of various PAHs from a soil matrix.

For instance, Sanders, *et al*. (1984) studied the dermal absorption of B(a)P and dimethylbenz(a)anthracene (DMBA) in Swiss-Webster mice from an acetone vehicle. The dermal absorption was similar for the two PAHs. For instance, at similar dose levels, the amount found in the tissues and excreta 24 hours after dosing was 84% for B(a)P and 82% for DMBA.

Yang and coworkers (Yang, *et al.* 1986a, 1986b) studied dermal absorption of B(a)P and anthracene at similar doses from solvent vehicles in the female Sprague-Dawley rat in both *in vivo* and *in vitro* systems. Absorption was similar for the two PAHs. *In vivo*, absorption after 144 hours was 46.2% for B(a)P and 52.3% for anthracene. *In vitro*, absorption after 144 hours was 49.9% for B(a)P and 55.9% for anthracene.

Ng and coworkers (Ng, *et al.*, 1992) studied dermal absorption of B(a)P and pyrene at similar doses from an acetone vehicle in the hairless guinea pig. Absorption after 24 hours was 73.3% for B(a)P and 93.9% for pyrene. In an *in vitro* experiment, absorption of B(a)P was 67.4% versus 89.9% for pyrene. In another *in vitro* experiment, absorption of B(a)P was 39.8% versus 40.8% for pyrene.

Dankovic and colleagues (Dankovic, *et al.,* 1989) studied the comparative dermal absorption in female CD-1 mice of 12 high molecular weight PAHs isolated from the 800-850 degree (F) complex organic mixture (COM) derived from a coal liquefaction process. Absorption was measured as the half-life of disappearance of the PAH from the mouse skin. The half-life was 5.0 hours for pyrene. For B(a)P, the half-life was 6.7 hours. All other PAH had half-lives similar to B(a)P, including benz(a)anthracene (6.5 hr), chrysene (7.3 hr), and benzo(j/k)fluoranthene (8.1 hr).

VanRooij, *et al.* (1995) studied the dermal absorption in the blood-perfused pig ear of 10 PAHs present in coal tar. The blood-perfused pig ear was chosen as a test system because pig skin resembles human skin morphologically and functionally and because percutaneous absorption rates of various chemicals in pig skin are comparable to the rates seen in human skin.

The absorption after 3.3 hours varied among PAHs. Absorption was greatest for phenanthrene and fluorene. Anthracene, fluoranthene, and pyrene showed similar absorption rates that were roughly ten times less than those for phenanthrene and fluorene. The 4-6 ring PAHs showed substantially lower dermal absorption, which was 100-1000 times less than that seen with phenanthrene and fluorene. It should be noted, however, that the maximum fractional absorption seen, which was with fluorene, was only 0.004% of the applied dose.

Of the potentially carcinogenic PAH studied in the above dermal absorption experiments, B(a)P showed equal or greater dermal absorption. None of these experiments were performed with soil matrices. They all involved applying the PAHs as solutions in organic solvents.

As noted above, dimethylbenz(a)anthracene, benz(a)anthracene, and benzo(b)fluoranthene were absorbed to a degree similar to B(a)P. Chrysene, benzo(k)fluoranthene, indeno[1,2,3-cd]pyrene, and dibenzo(a,h)anthracene were absorbed to a lesser degree than was B(a)P. Accordingly, it is health protective to use dermal-soil RAFs derived for B(a)P for performing a risk assessment of all potentially carcinogenic PAH.

Applicability to Non-Carcinogenic PAHs

Noncarcinogenic PAH with smaller molecular weights, however, were absorbed to a greater degree than was B(a)P in several experiments. Fluorene, phenanthrene, anthracene, fluoranthene, and pyrene were absorbed at rates varying from 1.03 times the B(a)P rate to 92 times the B(a)P rate. Accordingly it may be appropriate to modify upward the dermal-soil RAF derived from studies with B(a)P by the use of an uncertainty factor so that it can be used in the risk assessment of noncarcinogenic PAHs.

However, all of the experiments used coal tar or PAHs in solutions. No information is available on the comparative absorption of different PAHs from soil matrices. It is possible that small molecular weight PAHs in pure form are absorbed through skin to a greater degree than are large molecular weight PAHs, but that these smaller PAHs are also *less* bioavailable in soil matrices than are large PAHs. This could occur if the smaller PAHs more efficiently enter the small pore spaces of the soil matrices than do larger PAHs.

In the absence of appropriately designed experiments for noncarcinogenic PAH RAF derivation, it is difficult to determine a reasonable uncertainty factor. The dermal-soil RAF for noncarcinogenic PAHs may be higher or lower or the same as the dermal-soil RAF for potentially carcinogenic PAHs. The uncertainty factor is defined as a factor of 5. For deterministic risk assessments, the dermal-soil RAF for non-carcinogenic PAHs is 0.17 (i.e., the original four RAF estimates of 0.003, 0.009, 0.048, and 0.005, were each multiplied by 5, and the 90th percentile of the distribution of this data set was used as the point estimate).

3.4 Summary

Oral-Soil RAFs, potentially carcinogenic PAH

The 90th percentile PAH RAF value of 0.53 will be used as a conservative point estimates in the deterministic risk assessment, while the full distribution of PAH RAF values will be used in the probabilistic risk assessment. Figure 1 displays the cumulative probability distribution of RAFs for oral exposure to potentially carcinogenic PAHs in soil.

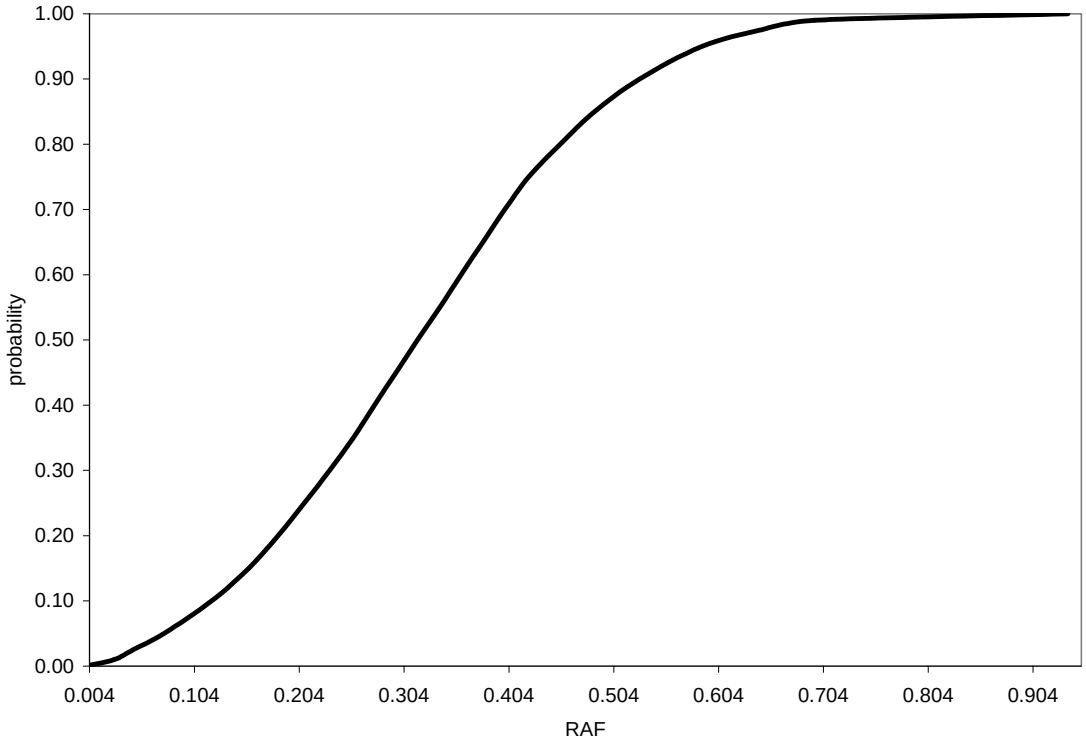

FIGURE 1
DISTRIBUTION OF ORAL-SOIL RAFs FOR POTENTIALLY CARCINOGENIC PAHs

Oral-Soil RAFs, non-carcinogenic PAH:
The 90th percentile PAH RAF value of 0.78 will be used as a conservative point estimates in the deterministic risk assessment, while the full distribution of PAH RAF values will be used in the probabilistic risk assessment. Figure 2 displays the cumulative probability distribution of RAFs for oral exposure to non-carcinogenic PAHs in soil.

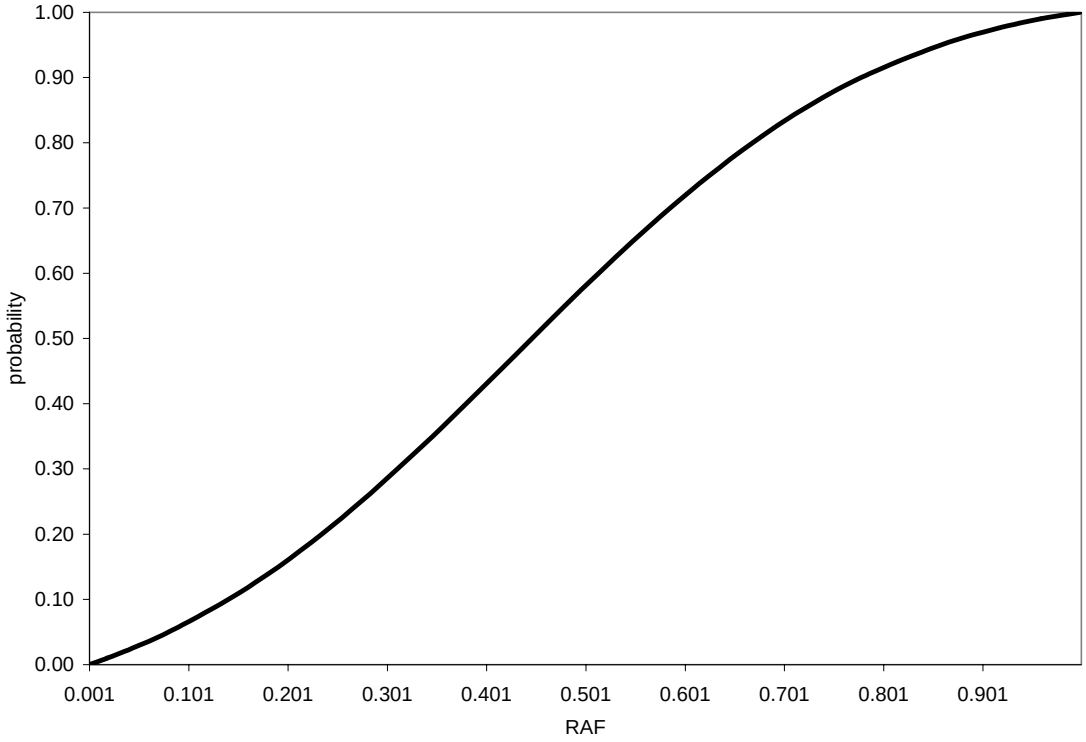

FIGURE 2
DISTRIBUTION OF ORAL-SOIL RAFs FOR NON-CARCINOGENIC PAHs

Dermal-Soil RAFs, potentially carcinogenic PAH:
The 90th percentile PAH RAF value of 0.03 will be used as a conservative point estimates in the deterministic risk assessment, while the full distribution of PAH RAF values will be used in the probabilistic risk assessment. Figure 3 displays the cumulative probability distribution of RAFs for dermal exposure to potentially carcinogenic PAHs in soil.

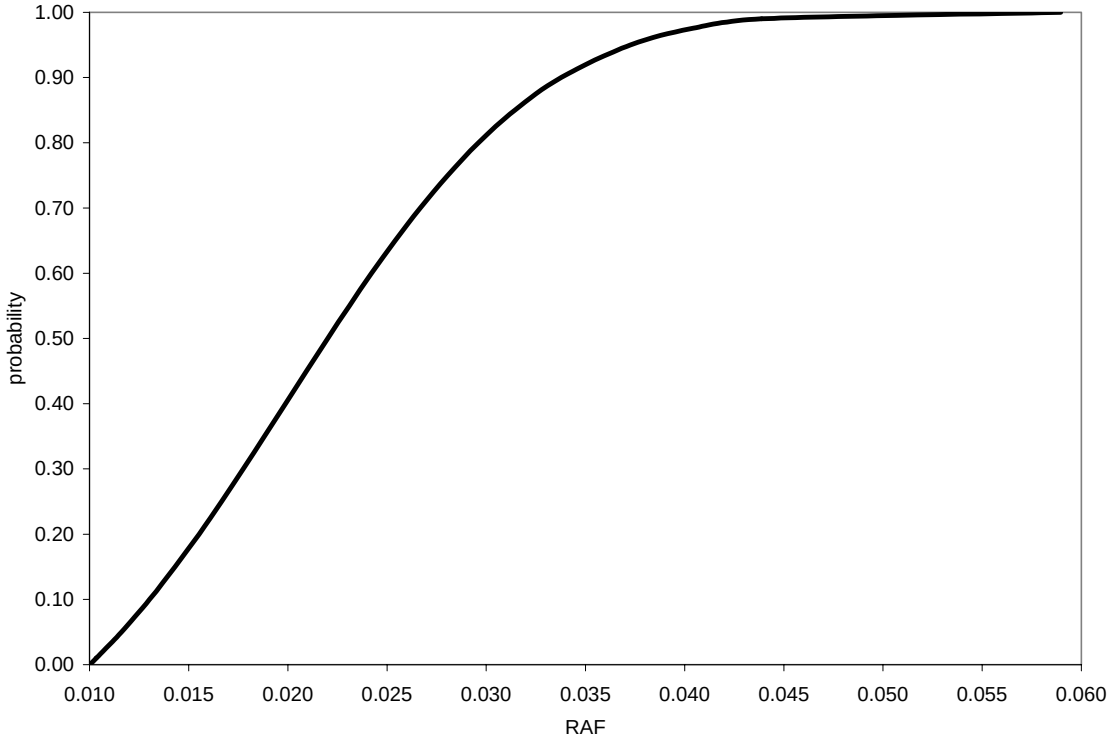

FIGURE 3
DISTRIBUTION OF DERMAL-SOIL RAFs FOR POTENTIALLY CARCINOGENIC PAHs

Dermal-Soil RAFs, non-carcinogenic PAH:
The 90th percentile PAH RAF value of 0.17 will be used as a conservative point estimates in the deterministic risk assessment, while the full distribution of PAH RAF values will be used in the probabilistic risk assessment. Figure 4 displays the cumulative probability distribution of RAFs for dermal exposure to non-carcinogenic PAHs in soil.

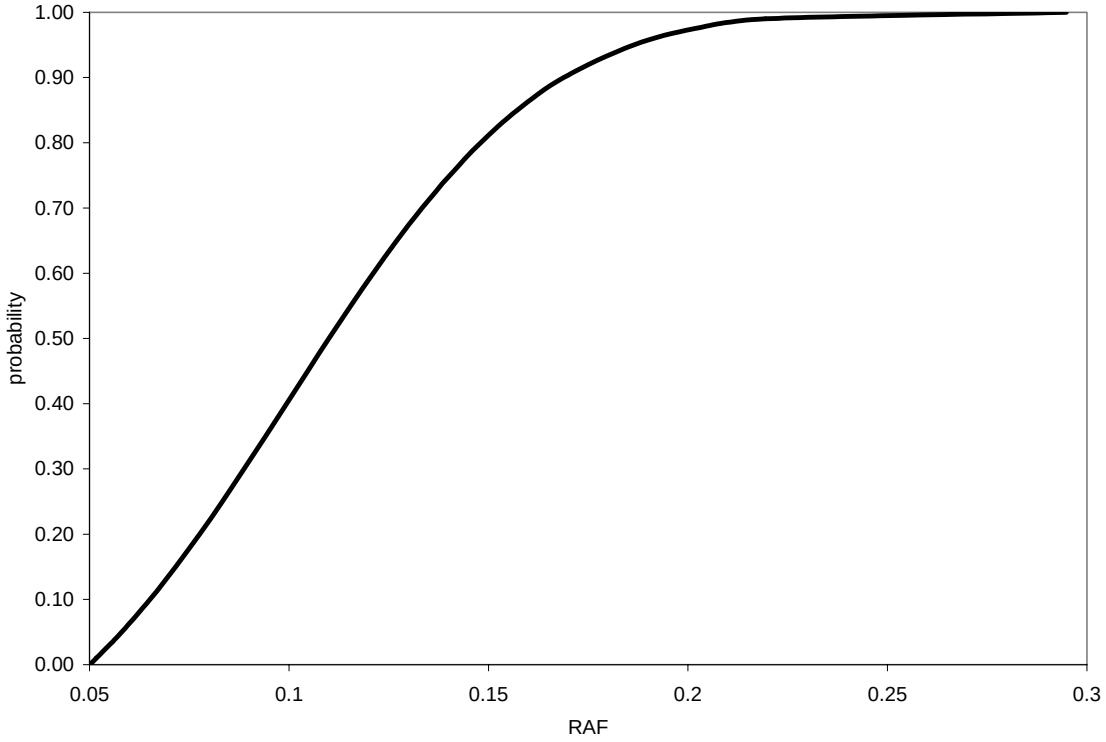

FIGURE 4
DISTRIBUTION OF DERMAL-SOIL RAFs FOR NON-CARCINOGENIC PAHs

4.0 TCDD-TEQ

4.1 Absorption in Dose-Response Studies

The oral CSF of 1.5×10^5 $(mg/kg/day)^{-1}$ for 2,3,7,8-TCDD is based on a dietary study in rats (Kociba, *et al*., 1978). The diet was prepared by mixing (30 minutes) an acetone solution of TCDD with laboratory chow. The acetone was evaporated yielding a TCDD/diet mixture. TCDD concentration was 0.02 - 2 ppb (0.001 - 0.1 ug/kg/da). No absorption information is given in the Kociba, *et al*. (1978) study.

In a study by Fries and Marrow (1975), however, rats were given TCDD in their diet continuously for 42 days. The total observation period of the experiment was 70 days. Diets were prepared in a similar manner to that used by Kociba, *et al*. (1978). Laboratory chow was mixed with a benzene solution of TCDD and the benzene was evaporated. Two dose levels were used, 7 ppb and 20 ppb. Absorption was reported to be 50-60%. For the purposes of RAF derivation, 55% was used as the observed absorption efficiency.

In several other studies, TCDD absorption was measured using vegetable oil and solvent vehicles. Gastrointestinal absorption from oil or solvent has been reported to range from 70% to >87%. AMEC assumes that 80% absorption occurred in corn oil studies as noted below. It is generally accepted that absorption for these vehicles is more efficient than absorption from diet. Thus, the results of the single dietary experiment (55%) will be used as an estimate of the absorption from the dietary dose-response study (Kociba, *et al*., 1978).

4.2 RAF for Oral Exposure to Soil

Several studies were identified that compared TCDD absorption from soil to either dirt, oil vehicle, or alcohol vehicle. These studies are relevant for derivation of the RAF. In the first study, Van den Berg and co-workers (1983) administered PCDDs and PCDFs from fly-ash and fly-ash extract to male Wistar rats as a dietary constituent. The fly-ash from a municipal incinerator in the Netherlands was chemically characterized and used.

Rats were fed treated diets for 19 days. The levels of PCDD and PCDF isomers in the liver at the end of the experiment were used as measures of absorption. By comparing fly-ash and fly-ash extract in a single experiment, the congener composition of the test material was held constant. Treatment of test diets with a PCDD/PCDF containing extract and evaporating the solvent is identical to the treatment of diets used by Kociba (1978) in the dose-response study. Thus, a comparison of the liver retention of PCDD/PCDF isomers with fly-ash-treated diet and extract-treated diet directly yields an estimate of the RAF (oral-fly-ash). AMEC assumed that the RAF (oral-soil) equals the oral fly-ash RAF.

The authors measured the liver levels of six isomer groups at the end of the experiment. From these data, AMEC calculated the fly-ash/extract ratio for each isomer group separately:

Liver concentration (ng/g)

	tetra-CDD	tetra-CDF	penta-CDD	penta-CDF	hexa-CDD	hexa-CDF
Fly-ash + diet (n=2)	0.8	3.5	2.7	11.0	5.2	13.6
Extract + diet (n=4)	1.9	14.5	18.9	50.0	47.7	83.3
Fly-ash/extract	0.42	0.24	0.14	0.22	0.11	0.16

The average fly-ash/extract ratio for all six isomer groups is 0.22. This is a direct measure of the degree to which adsorption to fly-ash decreases the bioavailability of PCDDs/PCDFs compared to pure compounds mixed with dietary constituents. Thus, the RAF (oral-fly-ash) is 0.22. Because fly-ash is a major source of TCDD equivalents in the environment, this data is relevant to risk assessment. Thus, one estimate of the RAF (oral-soil) is 0.22.

Several other studies are available in which absorption of TCDD from soil was compared to oil or alcohol vehicles. Results from these studies are useful if an independent estimate is available for gastrointestinal absorption of TCDD from the relevant vehicle.

McConnell, *et al*. (1984) investigated absorption in guinea pigs using soil from Missouri that was contaminated with TCDD. One or 3 ug/kg of TCDD was administered orally either in a corn oil vehicle or as a soil suspension. After a single dose of TCDD, the animals were observed for 30 days. The TCDD content of the liver was determined at 30 days or at the time of death of the animal. No detectible TCDD was observed in livers of animals dosed with 1 ug/kg of TCDD in either Times Beach or Minker Stout soil. At the higher dose level, TCDD was detected in animal livers with all groups. The liver levels in animals that survived for 30 days was lower than the levels in animals that died before completion of the experiment. Accordingly, the ratio of absorption from soil to absorption from corn oil for the latter group is higher: 0.24 for Times Beach and 0.15 for Minker Stout. The average ratio is 0.20.

It is well-documented that absorption of TCDD from vegetable oil vehicles exceeds the absorption from dietary constituents (U.S. EPA, 1985). As an estimate of the absorption of TCDD from vegetable oils, AMEC has averaged the results from the following four studies:

1. Rose, *et al*. (1976); rat; 1 μg/kg single dose; acetone/corn oil (1:25); 84%.
2. Rose, *et al*. (1976); rat; 0.1 or 1.0 μg/kg/da; acetone/corn oil (1:25); 5 days/week x 7 weeks; 86%.
3. Piper, *et al.* (1973); rat; 50 μg/kg single dose; acetone/corn oil (1:9); 70%.
4. Olson, *et al*. (1980); hamster; 650 μg/kg; olive oil; 74%.
5. Poiger and Schlatter (1986); human; 1 ng/kg; single dose; corn oil; >87%.

The average of these values is 80%. Thus, the RAF (oral-soil) using the McConnell, *et al*. (1984) data is defined as follows:

$$= (0.20) \times (0.8) / (0.55) = 0.29$$

This indirectly derived RAF (oral-soil) based on McConnell, *et al*. (1984) is in close

agreement with the value of 0.22 directly demonstrated by Van den Berg, *et al*. (1983).

In a similar experiment, Poiger and Schlatter (1980) studied the effects of soil adsorption on the bioavailability of TCDD in Sprague-Dawley rats. After oral administration of 15 ng radiolabelled TCDD using 50% ethanol as a vehicle, 37% of the dose was detected in the liver 24 hours later. When the constituent (21-22 ng) was administered as an aqueous suspension of soil particles (37% w/w) that had been in contact with the TCDD for 8 days, the fraction of the administered dose that was found in the liver 24 hours later was 16%. From these data, the ratio of TCDD absorption from soil compared to an aqueous ethanol vehicle is 0.43.

There are no estimates available for absorption of TCDD from 50% ethanol vehicles. To derive an estimate of the RAF (oral-soil) from the Poiger and Schlatter data, AMEC assumed that the absorption of TCDD from 50% ethanol is the same as the average absorption reported from corn oil, olive oil, 1:25 acetone/corn oil, and 1:9 acetone/corn oil. The RAF (oral-soil) is derived as above: (0.43) x (0.8)/(0.55) = 0.63.

Similar studies have also been performed in rabbits by Bonaccorsi, *et al*. (1984). Levels of TCDD in the liver 7 days after an oral dose of TCDD either in alcohol or in soil from Seveso, Italy were compared. The ratio of TCDD absorption from soil relative to alcohol vehicle was 0.32 in this study. As above, AMEC assumed that the absorption of TCDD from alcohol vehicle is 80%. Thus, the RAF (oral-soil) is (0.32) x (0.80)/(0.55) = 0.47.

In addition, Lucier, *et al*. (1986) fed female Sprague-Dawley rats TCDD in either corn oil or contaminated soil from the Minker site in Missouri. Eight doses ranging from 0.015 to 5 ug TCDD/kg were administered. Soil was passed through a 60 gauge sieve before use. Doses of TCDD in corn oil or soil were administered by gavage. Six days after treatment, the animals were sacrificed and the TCDD content in the livers was measured.

TCDD-CORN OIL **TCDD-SOIL**

DOSE LEVEL	**CONC. IN LIVER**	**DOSE LEVEL**	**CONC. IN LIVER**
5 ug/kg	40.8 ppb	5.5 ug/kg	20.3 ppb
1 ug/kg	7.6 ppb	1.1 ug/kg	1.8 ppb

CONCENTRATIONS NORMALIZED TO CORN OIL DOSE LEVELS

DOSE LEVEL	CORN OIL CONC. IN LIVER	SOIL CONC. IN LIVER	SOIL/CORN OIL
5 ug/kg	40.8 ppb	18.5 ppb	0.45
1 ug/kg	7.6 ppb	1.64 ppb	0.22

The average of the two soil-to-corn oil ratios is 0.34. As above, AMEC assumed that the absorption of TCDD from a corn oil vehicle is 80%. Thus, the RAF (oral-soil) is (0.34) x (0.80) / (0.55) = 0.49.

Shu, *et al*. (1988) measured bioavailability of TCDD in the rat. Three soil samples were collected from areas of Times Beach. TCDD concentrations were 723 ppb, 28.6 ppb, and 1.9 ppb. Male Sprague-Dawley rats were administered TCDD by gavage. 24 hours after dosing, the rats were sacrificed and the levels of TCDD were measured in the livers. Six groups of animals, containing four rats per group were dosed by gavage with TCDD in soil at 3.2, 7.0, 37, 40, 175, and 1450 ng/kg of TCDD. Control rats were dosed with TCDD dissolved in corn oil at 2.0, 8.5, 32, 40, 200, and 1180 ng/kg.

The concentrations of TCDD in the livers of the corn oil groups were adjusted to 100% bioavailability assuming, based on Piper, *et al*., (1973), that absorption of TCDD from corn oil is 70%. Then, the liver concentrations from the soil groups were compared to the adjusted liver concentrations from the corn oil groups to derive estimates of bioavailability. The values reported by Shu, *et al*. (1988) are thus estimates of absolute bioavailability. The values varied from 37% to 49% and were not dose-dependent. The average absolute bioavailability was 43%.

The bioavailability relative to the dose-response study is the RAF (oral-soil). This is calculated as follows: (0.43) x (100%)/(55%) = 0.78.

Umbreit, *et al*. (1987) fed soil containing TCDD from Times Beach Missouri and Newark, NJ to male and female rats as suspensions by gavage either for one or for four consecutive days. Total TCDD doses administered to rats were either 10 ug TCDD/kg or 40 ug TCDD/kg. Rats were sacrificed after the fnal dose, autopsied, and hepatic microsomal fractions were collected. Aryl hydrocarbon hydroxylase (AHH) levels were determined in the microsomes. In addition, the same dose of TCDD was added to clean soil in acetone and used immediately as a control. Each treatment group had four animals. The ratio of AHH activity in the aged soils to the AHH activity in the freshly prepared soil is a measure of relative bioavailability. The ratios for the four experiments were 0.35, 0.46, 0.56, and 0.52. The average of these four ratios, 0.47, is an estimate of the RAF (oral-soil).

Umbreit, *et al*. (1986) fed soil containing TCDD from two sites in Newark, NJ to guinea pigs and measured the TCDD in their livers 60 days after dosing. The authors estimated that the bioavailability was 0.5% in one soil and 21.3% in the second soil. The

average bioavailability is 0.11. AMEC assumes that these values are estimates of absolute bioavailability. The bioavailability relative to the dose-response study is the RAF (oral-soil). This is calculated as follows: (0.11) x (100%)/(55%) = 0.20.

Wittsiepe, *et al*. (2007) studied the oral bioavailability of seventeen 2,3,7,8-chlorosubstituted dioxin/furan congeners from soil in minipigs. The total PCDD/F concentration in soil was 5.3 μg TEq/kg. Bioavailability of PCDD/F from soil was calculated by examining the retention of PCDD/F congeners in liver, adipose tissue, muscle, brain, and blood. Based on the concentrations retained in the above tissues, the bioavailability of individual PCDD/F congeners from soil ranged from 0.0064 to 0.219, with a mean of 0.091. On a toxic equivalents basis, the bioavailability of PCDD/F from soil was determined to be 0.138. Because human health risk assessments are performed for 2,3,7,8-TCDD TEQ, the value normalized to 2,3,7,8-TCDD toxic equilvalents is appropriate for Table 11.

The following table summarizes all of the RAF (oral-soil) estimates that are discussed above. The average of all eight estimates is 0.40.

TABLE 11
ORAL-SOIL RAFS FOR 2,3,7,8-TCDD

SOURCE	ESTIMATE FOR ORAL-SOIL RAF
Poiger and Schlatter (1980)	0.63
Van den Berg, *et al*. (1983)	0.22
McConnell, *et al*. (1984)	0.29
Bonaccorsi, *et al*. (1984)	0.47
Lucier, *et al*. (1986)	0.49
Umbreit, *et al*. (1986)	0.20
Shu, *et al*. (1988)	0.78
Wittsiepe, *et al*. (2007)	0.138

The 90th percentile of the eight estimates of the RAF (oral-soil) is 0.50 (calculated from the full distribution of results using @RISK® software and assuming data are lognormal). This value is more health-protective than the bioavailability factor of 30% used in the Center for Disease Control's risk assessment of TCDD in soil (Kimbrough, *et al*. 1985). Thus, the RAF (oral-soil) for the deterministic assessment is 0.50.

4.3 RAF for Dermal Exposure to Soil

To derive the RAF (dermal-soil) one needs a value for the efficiency of absorption of soil-bound TCDD through human skin and an estimate of the absorption efficiency from dietary constituents in the Kociba study. As discussed above, the gastrointestinal absorption of TCDD by rats from diet was found to be 55% by Fries and Marrow (1975). Several studies have been performed to determine such absorption of TCDD from various matrices. These will be used in the RAF derivation.

Roy, *et al*. (1990) measured the dermal bioavailability of neat 2,3,7,8-tetrachloro-dibenzo-p-dioxin (TCDD) and TCDD adsorbed on soils in an EPA-funded study. Parallel experiments were carried out with female Sprague-Dawley rats, in vivo and in vitro, and with human skin specimens, in vitro. Adsorption of TCDD on low organic soil (0.77% organic matter) at 1 ppm dramatically reduced the dermal bioavailability of TCDD. The soil application rate was 10 mg/cm^2. The fraction of applied dose absorbed was decreased by a factor of five to ten compared to experiments with neat TCDD at an equivalent dose. Penetration of low organic soil-sorbed TCDD through human skin was approximately three times less than for rat skin.

The RAF (dermal-soil) was calculated several ways for TCDD. In all cases, the RAF is defined as (absorption from soil)/(absorption from diet). AMEC assumes that a relevant exposure time for soil contact was several hours. To be health-protective, however, 8-hour exposures are assumed for purposes of deriving the RAF.

Roy and co-workers found that 33% of 10 ng/cm^2 of TCDD (neat) was dermally absorbed by the rat over 8 hours. This was determined *in vivo*. In addition, after 96 hours 77.4% was absorbed in an *in vivo* experiment, and 76% was absorbed in an *in vitro* experiment (average 76.5%). Thus, 8-hour absorption was 43% of the 96-hour absorption. When the same amount of TCDD was applied to the rat in low organic soil, 16.3% was absorbed in 96 hours *in vivo* and 7.7% was absorbed in vitro (average 12.0%). The TCDD concentration in soil (1 ppm) and the soil contact rate (10 mg/cm^2) are both relevant for use in risk assessment. When the same dose in low organic soil was applied to human skin *in vitro*, 2.4% was absorbed after 96 hours. The same dose was also applied in high organic soil to rat skin *in vitro*, and absorption after 96 hours was 1.0%.

First, AMEC derived a RAF (dermal-soil) from the in vitro human skin experiment. Here, the absorption of TCDD from low organic soil over 96 hours was 2.4%. Because there are no data for 8-hour exposures, AMEC assumes that the amount absorbed in 8 hours was 43% of the amount absorbed in 96 hours. The RAF, then, is (2.4%)(0.43)/(55%) = 0.02.

Second, AMEC derived an RAF (dermal-soil) from both the in vivo and in vitro rat experiments using low organic soil. At 96 hours, the absorption of TCDD from low organic soil was 16.3% *in vivo* and 7.7% *in vitro*. AMEC assumes tht the amount absorbed in 8 hours was 43% of the amount absorbed in 96 hours. Thus, the *in vivo* rat RAF is (16.3%)(0.43)/(55%)= 0.13. The *in vitro* rat RAF is (7.7%)(0.43)/(55%) = 0.06.

Third, AMEC derived an RAF (dermal-soil) frrom the *in vitro* rat experiment using high organic soil. At 96 hours, the absorption of TCDD from high organic soil was 1.0%. As

above, the RAF is (1.05%)(0.43)/(55%)= 0.01.

In addition to the recent study of Roy, *et al*. (1990), a study by Poiger and Schlatter (1980) has been widely used by risk assessors. Poiger and Schlatter (1980) dosed hairless rats (Naked ex Back-Cross and Holzman strain) with radiolabelled TCDD. The fraction of the administered dose in the liver after 24 hours was compared for two situations:

1. 26 ng pure TCDD per 3 cm^2 of skin; and
2. 26, 350 or 1,300 mg TCDD in a soil/water paste of 75 mg per 3-4 cm^2 of skin (50 mg dry soil/3-4 cm^2).

The fraction of the dose in the liver after administration of the soil paste was near the detection limit for the low dose and the same for the two higher dose levels. AMEC averaged the values and compared them to the percent dose in the liver following administration of pure TCDD to determine the ratio: (absorption from soil, 24 hours)/(absorption neat, 24 hours) = (1.32%)/(14.8%) = 0.09. However, one cannot obtain an estimate of the actual fraction of a dose of pure TCDD that is absorbed in 8 hours from this experiment. Thus, the estimate of the dermal absorption of pure TCDD over 8 hours provided by the Roy, *et al*. (1990) study was used in RAF derivation:

RAF (dermal-soil) = [(0.09) x (0.33)]/(0.55) = 0.05

In addition, another estimate of 8-hour dermal absorption of pure TCDD was used. Banks and Birnbaum (1990) measured absorption of 3 ug radiolabelled TCDD/cm^2 in 10-week old male Fischer 344 rats at various time points up to 48 hours. Absorption was linear to 48 hours with a rate of 0.5 ng/hr. Predicted absorption at 8 hours was 6.6% (actual data point at 8 hours was 5.5%). Thus, the estimate of the dermal absorption of pure TCDD over 8 hours provided by the Banks and Birnbaum (1990) study was used in RAF derivation:

RAF (dermal-soil) = [(0.09) x (0.066)]/(0.55) = 0.01

Shu, *et al*. (1988) also measured the dermal absorption of TCDD from a soil matrix in male Sprague-Dawley rats. Soil samples were obtained from Verona and Times Beach, MO. The soil was air-dired and sieved through 10-, 20-, and 40-mesh screens. Laboratory samples were prepared by adding tritiated TCDD in hexane:methylene chloride (7:3, v:v) at concentrations of 10 ppb and 100 ppb. The actual environmental oil sample was a sample from Times Beach, MO containing 123 ppb TCDD. TCDD-containing soil was administered onto the backs of the rats (0.25 g soil/12 cm^2). A nonocclusive cover was placed over the area. The dose remained in contact with the skin for 24 hours. After 48 hours, the animals were sacrificed and the livers were analyzed for TCDD levels.

The level of TCDD in the liver of rats given soil-bound TCDD dermally was compared to the levels of TCDD in the livers of rats given the TCDD orally dissolved in corn oil, after normalizing the corn oil data to account for the absorption of 70% as discussed in Shu, *et al*. (1988). This ratio provides an estimate of the bioavailability relative to corn oil gavage. The RAF (dermal-soil) then must be derived which compares the bioavailability to the dose-response study, which was a dietary feeding study.

The data from 24 hour dosing studies were used, because the study provided no basis for estimating the absorption at 8 hours. In fact, the absorption at 4 hours was found to be 60% of the absorption seen at 24 hours, indicating that dermal penetration was not linear in this experiment. Accordingly, AMEC assumes that 100% of the absorption measured at 24 hours had, in fact, occurred by 8 hours. This assumption is health-protective.

TCDD CONCENTRATION (ppb)	**ADMINISTERED DOSE IN LIVER RELATIVE TO CORN OIL GAVAGE**
10 ppb (laboratory sample)	1.14%
100 ppb (laboratory sample)	1.5%
123 ppb (Times Beach environmental sample)	1.6%

The estimates of the dermal-soil RAF are derived as follows:

(1.14%)/(55%) = 0.02
(1.5%)/(55%) = 0.03
(1.6%)/(55%) = 0.03

In conclusion, AMEC has derived nine estimates of the RAF (dermal-soil). These estimates agree well:

1. Roy, *et al*. (1990), human, *in vitro*; RAF = 0.02.
2. Roy, *et al*. (1990), rat, *in vivo* (low organic soil); RAF = 0.13.
3. Roy, *et al*. (1990), rat, *in vitro* (high organic soil); Banks and Birnbaum (1990), rat, in vivo, RAF = 0.01.
4. Roy, *et al*. (1990), rat, *in vitro* (low organic soil); RAF= 0.06.
5. Poiger and Schlatter (1980), rat, *in vivo*; Roy et al. (1990), rat, in vivo; RAF= 0.05.
6. Poiger and Schlatter (1980), rat, *in vivo*; Banks and Birnbaum (1990), rat, in vivo; RAF = 0.01.
7. Shu, *et al*. (1988), rat, *in vivo* (10 ppb); RAF = 0.02.
8. Shu, *et al*. (1988), rat, *in vivo* (100 ppb); RAF = 0.03.
9. Shu, *et al*. (1988), rat, *in vivo* (123 ppb); RAF = 0.03.

AMEC uses the 90th percentile of these nine estimates as the RAF (dermal-soil) for the deterministic assessment = 0.08 (calculated from the full distribution of results using @RISK® software and assuming data are exponential).

4.4 Summary

Oral-Soil RAFs, Dioxins:
The 90th percentile dioxin RAF value of 0.50 will be used as a conservative point estimates in the deterministic risk assessment, while the full distribution of dioxin RAF values will be used in the probabilistic risk assessment. Figure 5 displays the cumulative probability distribution of RAFs for oral exposure to dioxins in soil.

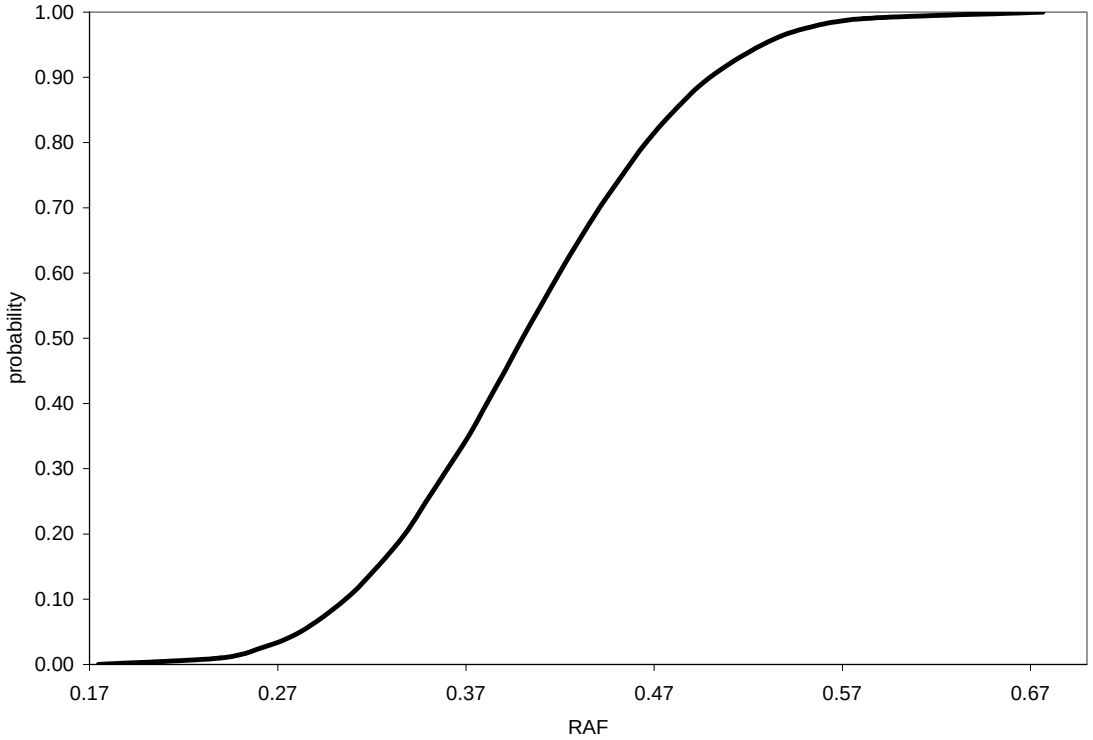

FIGURE 5
DISTRIBUTION OF ORAL-SOIL RAFs FOR DIOXIN

Dermal-Soil RAFs, Dioxins:

The 90th percentile dioxin RAF value of 0.08 will be used as a conservative point estimates in the deterministic risk assessment, while the full distribution of dioxin RAF values will be used in the probabilistic risk assessment. Figure 6 displays the cumulative probability distribution of RAFs for dermal exposure to dioxins in soil.

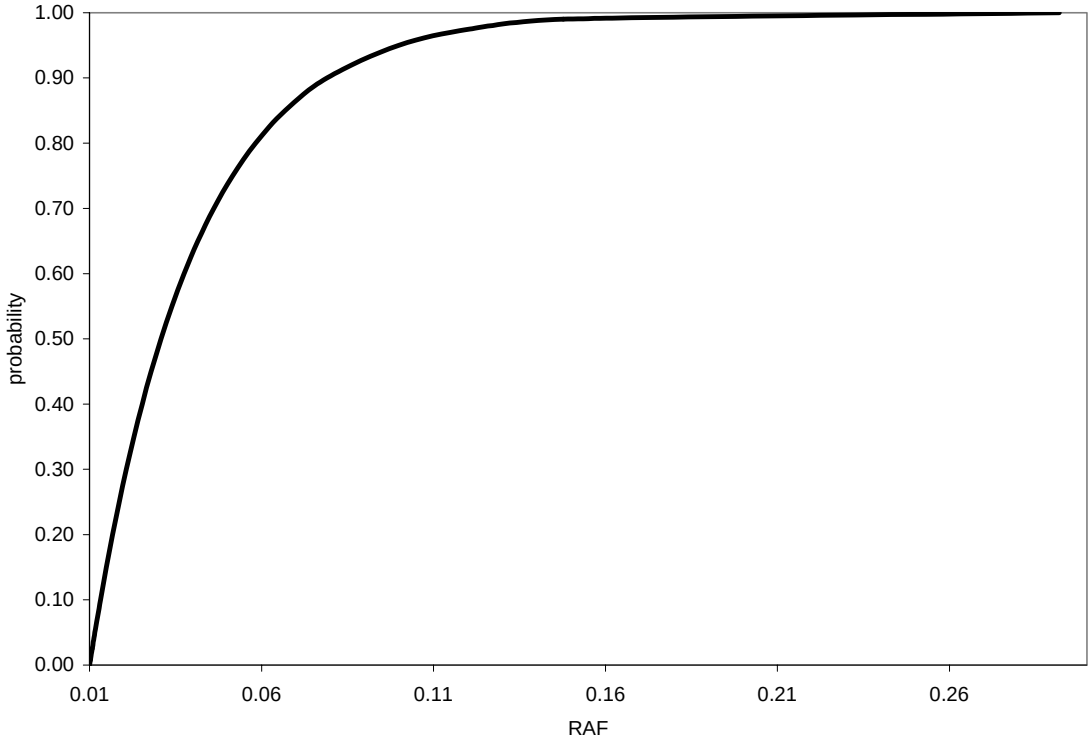

FIGURE 6
DISTRIBUTION OF DERMAL-SOIL RAFs FOR DIOXIN

5.0 Arsenic

The oral reference dose for noncarcinogenic effects of arsenic is 3E-04 mg/kg-day, and the oral cancer slope factor for carcinogenic effects is 1.5 per mg/kg-day (IRIS-U.S. EPA, 2001). Both values are based on epidemiological studies that characterized health effects in a large population of Taiwanese who consumed drinking water containing arsenic. The exact form of the ingested arsenic is unknown.

5.1 Absorption in Dose-Response Studies

The relevant dose-response study characterized health effects in a large population of Taiwanese who consumed drinking water containing arsenic. Several studies investigating the absorption of arsenic have been performed in humans and various animal species. Human studies are sufficiently extensive to strongly suggest that close to 100% of soluble inorganic arsenic in water is absorbed from the gastrointestinal tract. These human studies are reviewed in detail here.

One direct indication of absorption of an orally administered dose of a chemical is its urinary excretion. Several studies show that urinary excretion can account for the majority of an orally administered dose of arsenic. Buchet, *et al*. (1981a) administered aqueous sodium arsenite (NaAsO2) as a single dose to three human volunteers. An average of 45% of the dose was excreted in the urine in four days. In a second study (Buchet, *et al*., 1981b), four individuals given 125, 250, 500, or 1000 Ug As/day orally for five days excreted 54, 73, 74, and 64% of the dose in urine, respectively, over 14 days. The average urinary excretion of arsenic for the four subjects was 66% of the administered dose. Crecelius (1977) reports that approximately 50% and 80% of orally administered aqueous arsenic was excreted in urine within 61 hours by a single individual in two experiments. The results of these studies represent the minimum amount of arsenic absorbed since the balance of the dose was not accounted for.

Data for human fecal excretion of arsenic do exist. Pomroy, *et al*. (1980) gave 6 male subjects radiolabelled arsenic acid ($[^{74}As]H_3AsO_4$) in gelatin capsules followed by a glass of water. The presence of arsenic in the body, urine, and feces was measured using a whole body radiation counter. The authors report that for the six subjects the average total excretion over 7 days was 6.1$\pm$2.8% in feces. It is not possible to determine how much of this arsenic was first absorbed and then excreted. The total recovery of arsenic (urine plus feces) was 68.4$\pm$4.0% of the single oral dose. The remaining arsenic was reported to be present in the body tissues; virtually the entire dose could be accounted for. This suggests a minimum absorption of 94% (100% - 6%) of orally ingested arsenic.

A study by Bettley and O'Shea (1975) also reports excretion of arsenic in both urine and feces. Three subjects were exposed to 8.52 mg As (as 1.25 ml of Liq. Arsenicalis B.P.) in three portions 8 hours apart on one day. They found that at most 3.5% of the dose was excreted in feces over ten days. This suggests a minimum absorption of 96%. Urinary excretion averaged 52$\pm$4% of the exposure dose over 10 days (n=3). The remaining half of the dose was unaccounted for, although small amounts of arsenic were found in blood and hair.

In the Coulson study (Coulson, *et al*., 1935), results from two humans each ingesting two forms of arsenic are reported. Less than 5% of an oral dose was excreted in feces whether

the arsenic was taken as arsenic trioxide (As_2O_3) or as natural arsenic present in shrimp. The remainder of the dose, more than 95%, was recovered in urine in three experiments where total recoveries ranged from 74 to 115%. Based on the fecal excretion data from this study, it can be estimated that at least 95% of the ingested arsenic was absorbed. The fecal excretion data are consistent with those of Pomroy, *et al*. (1980) and Bettley and O'Shea (1975).

Fecal excretion data from oral studies provide a minimum estimate of absorption, because it cannot be determined how much of the dose was first absorbed and then excreted into the feces. However, a study in humans injected intravenously with arsenic suggests that absorbed arsenic may be excreted, presumably from bile, into the feces. Mealy, *et al*. (1959) administered radiolabelled arsenic by intravenous injection. Between 57% and 90% of the injected dose was recovered in urine in 10 days. Fecal excretion accounted for 1.3% of the dose after seventeen days in one individual. A second subject excreted 0.2% of the intravenous dose into the feces in one week. Both results indicate some excretion of arsenic into the feces. Virtually all of the remaining dose was recovered in the urine. Biliary excretion of arsenic has been demonstrated in rats, rabbits, and dogs (Klaassen, 1974; Gregus and Klaassen, 1986). This indicates that a portion of the arsenic found in feces in studies using oral dosing may have been first absorbed and then excreted.

The urinary excretion data from the oral studies discussed above provide minimum estimates of arsenic absorption ranging from 45% to 95%. The fecal excretion data suggest that, at a minimum, 95-96% of an orally administered dose of arsenic is absorbed. The study of intravenously administered arsenic suggest that biliary excretion can occur. Therefore, it can conservatively be concluded from the above studies that virtually 100% of an orally administered dose of soluble inorganic arsenic can be absorbed in humans.

5.2 RAF for Oral Exposure to Soil

The oral-soil RAF for arsenic is defined as: (absorption of arsenic in humans from ingested soil) / (absorption of arsenic in humans in the epidemiological study from ingested water). There are many forms of inorganic arsenic, and these have widely varying solubilities. While it is appropriate to assume that arsenic present in water would be a soluble form of arsenic, this is not necessarily the case for arsenic present in soil or ash. Arsenic present in soils can either be in a relatively insoluble mineral form, such as would be expected in slags, mine tailings, and ash; or, the arsenic can be present in a more soluble form such as might be present at hazardous waste sites where arsenic salts were either disposed of or accidentally released. Even soluble species, however, become bound tightly to soils after years of weathering.

A number of RAFs for oral exposure to arsenic in soil are available in the literature. Roberts, *et al*. (2002), however, has identified an RAF specifically for exposure to soil from sites in Florida, including a wood treatment site in Gainesville, Florida. Therefore, this RAF was given precedent in the deterministic assessment.

Roberts, et al. (2002) Study

Roberts, *et al*. (2002) measured arsenic bioavailability from soils affected by releases of soluble arsenic salts in Cebus apella monkeys in a study for the Florida Department of Environmental Protection. Soil samples were taken from five sites with arsenic

contaminated soil from different sources, but all from arsenical salts: (1) electrical substation, (2) cattle dip site, (3) pesticide site #1, (4) wood treatment site, and (5) pesticide site #2. Relative bioavailability was assessed based on urinary excretion following an oral dose in solution. Relative bioavailability for the five sites was: (1) 0.146 +/ 0.05, (2) 0.247 +/- 0.03, (3) 0.107 +/- 0.05, (4) 0.163 +/- 0.07, and (5) 0.17 +/- 0.10. The mean of these five soil types was 0.17. Relative bioavailability of the soil from the wood treatment site was 0.16.

Summary

The RAF of 0.16 for soil from a wood treatment site in Florida (Roberts, *et al*. 2002) is directly relevant to the risk assessment of a wood treating site in Gainesville, Florida. Thus, the 0.16 value will be used for the Gainesville risk assessment for the deterministic assessment. The probabilistic assessment will employ a distribution of RAFs based upon the results of the Roberts, *et al*. (2002) study.

5.3 RAF for Dermal Exposure to Soil

The RAF (dermal-soil) for this chemical is defined as: (absorption in humans from dermal contact with soil) / (absorption of arsenic in humans in the epidemiological study from ingested water). The RAF (dermal-soil) of 0.009 is derived below.

To derive the RAF (dermal-soil), AMEC uses the estimates of the fractional dermal absorption of arsenic from soil reported by Wester, *et al*. (1993). Wester, *et al*. (1993) measured the skin uptake of soluble arsenic (H_3AsO_4) from soil in monkey skin *in vivo* and in human skin *in vitro*. Radiolabelled arsenic was mixed with Yolo County 65-California-57-8 soil at two concentrations: 0.001 mg/kg and 15 mg/kg. The soil retained by an 80-mesh sieve was 26% sand, 26% clay, 48% silt, and 0.9% organic matter. Soil load on the skin was 40 mg/cm^2. For each dose of arsenic, four female Rhesus monkeys were administered the arsenic containing soil on abdominal skin. The area was covered with a nonocclusive cover. After 24 hours, the soil was removed from the skin, and the area was washed with soap and water. Urine was collected for 7 days. *In vivo* percutaneous absorption was determined by the ratio of urinary excretion following topical administration to that following intravenous administration. Percutaneous absorption of arsenic from soil was 4.5 +/- 3.2% from the low dose and 3.2 +/- 1.9% from the high dose. Soap and water washes removed most of the admistered dose after the 24 hour exposure period.

Percutaneous absorption was also measured in viable human cadaver skin dermatomed to 500 um. The skin was preserved and used within five days of collection. Measurements were taken in triplicate for each of three skin samples. The arsenic dose was 0.001 mg/kg and the soil loading was 40 mg/cm^2. After a 24-hour exposure period, the amount of arsenic present in the receptor fluid (phosphate buffered saline) plus the amount in the skin that was not removed by a surface wash was 0.76% of the administered dose.

The dermal-soil RAF is calculated by using all three results from Wester, *et al*. (1993):

4.5% monkey *in vivo*, low dose
3.2% monkey *in vivo*, high dose
0.8% human *in vitro,* low dose

The average fractional absorption over 24 hours is 2.8%. Typical exposures at industrial sites are not 24 hours in length. Thus, the above data are prorated to a more reasonable exposure period of 8 hours. The average fractional absorption over 8 hours is 0.94%. The 90th percentile of the dermal-soil RAF is 0.01 (calculated from the full distribution of results using @RISK® software and assuming data are normal).

5.4 Summary

Oral-Soil RAFs, Arsenic:
The RAF value of 0.16 from Roberts, *et al*. (2002) will be used as a conservative point estimate in the deterministic risk assessment, while the full distribution of arsenic RAF values (generated using the mean and standard deviation for the wood-treating site from Roberts, *et al*. (2002)) will be used in the probabilistic risk assessment. Figure 7 displays the cumulative probability distribution of RAFs for oral exposure to arsenic in soil.

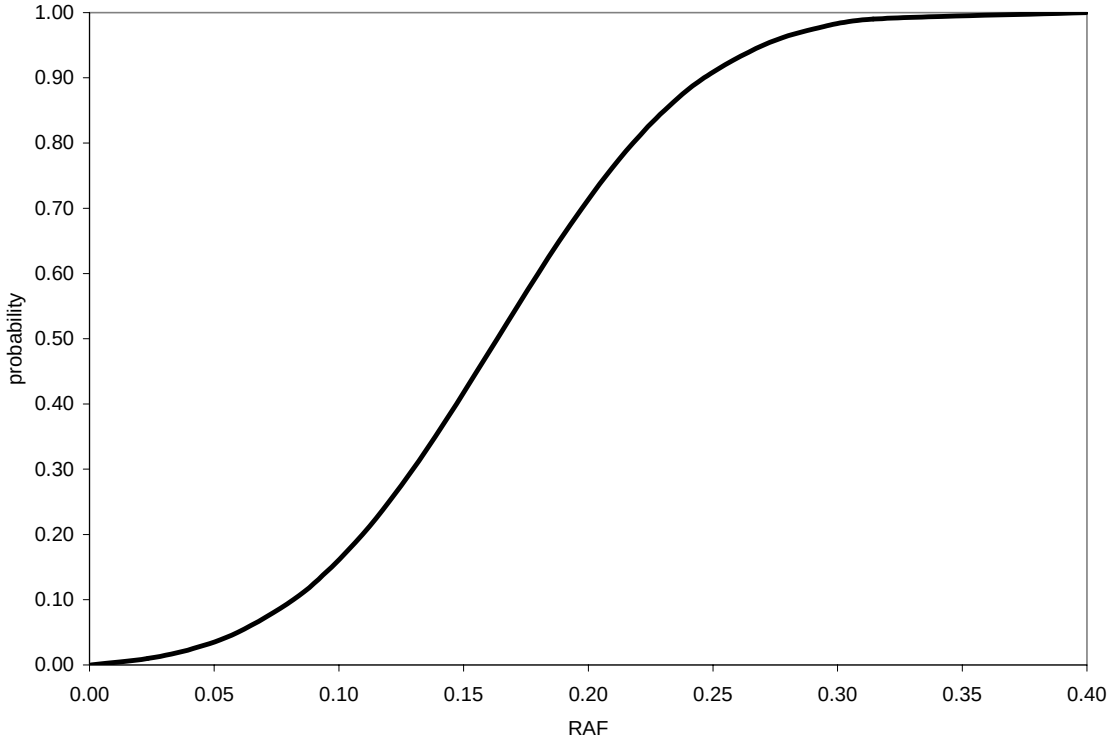

FIGURE 7
DISTRIBUTION OF ORAL-SOIL RAFs FOR ARSENIC

Dermal-Soil RAFs, Arsenic:

The 90th percentile arsenic RAF value of 0.01 will be used as a conservative point estimates in the deterministic risk assessment, while the full distribution of arsenic RAF values will be used in the probabilistic risk assessment. Figure 8 displays the cumulative probability distribution of RAFs for dermal exposure to arsenic in soil.

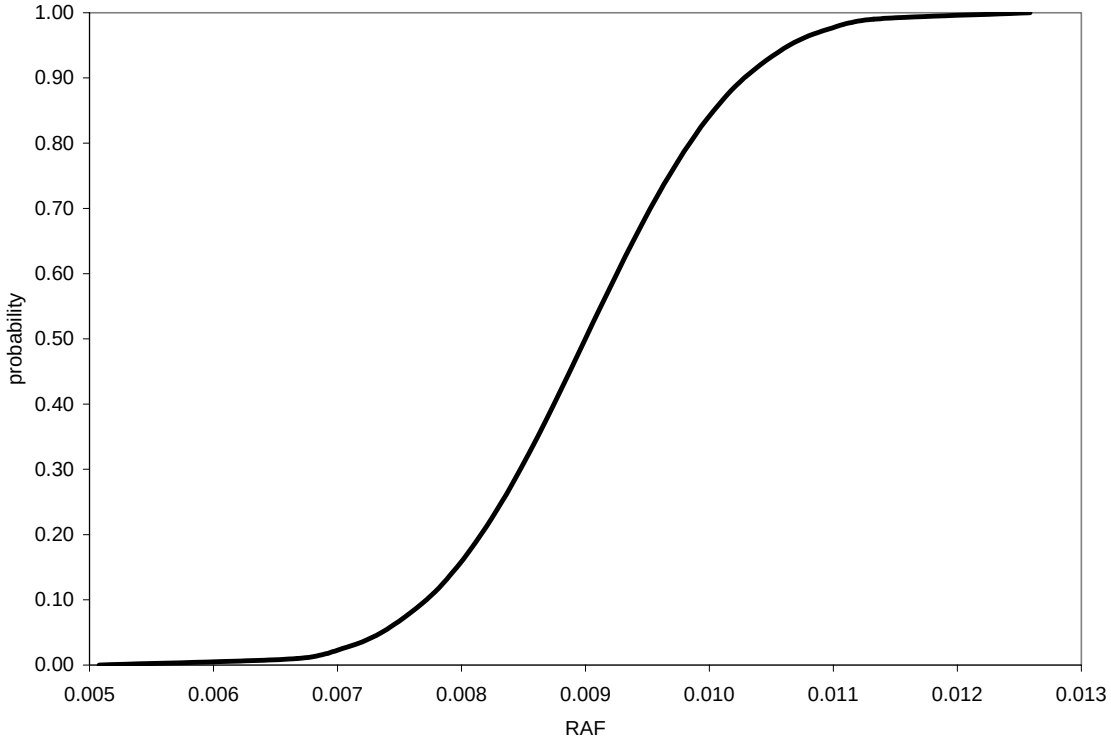

FIGURE 8
DISTRIBUTION OF DERMAL-SOIL RAFs FOR ARSENIC

6.0 References

Banks, Y.B. and L.S. Birnbaum. 1990. Finite Dermal Absorption After Low-Dose TCDD Exposure. Toxicologist 10:309.

Bartosek, I., Guitani, A., Modica, R., Fiume, M., and Urso, R. 1984. Comparative Kinetics of Oral Benz(a)Anthracene, Chrysene, and Triphenylene in Rats: A Study with Hydrocarbon Mixtures. Toxicology Letters 23:333-339.

Bettley, F.R. and J.A. O'Shea. 1975. The Absorption of Arsenic and Its Relation to Carcinoma. British Journal of Dermatology. (92):563-568.

Bonaccorsi, A., di Domenico, A., Fanelli, R., Merli, F., Motta, R., Vanzati, R., and Zapponi, G.A. 1984. The Influence of Soil Particle Adsorption on 2,3,7,8-Tetrachlorodibenzo-p-dioxin Biological Uptake in the Rabbit. *Arch. Toxicol. Suppl.* 7:431-434.

Bonaccorsi, A., A. DiDomencio, F. Fanelli, F. Merli, R. Motta, R. Vanzati and G.A. Zapponi. 1984. The influence of soil particle adsorption on 2,3,7,8-TCDD biological uptake in the rabbit. Arch. Toxicol. Suppl. 7:431-434.

Bordelon, N.R., Donnelly, K.C., King, L.C., Wolf, D.C., Reeves, W.R., and George, S.E. 2000. Bioavailability of the genotoxic components in coal tar contaminated soils in Fischer 344 rats. *Toxicological Sciences*. 56: 37-48.

Bowes, S.G. and Renwick, A.G. 1986. The hepatic metabolism and biliary excretion of benzo[a]pyrene in guinea-pigs fed normal, high-fat or high-cholesterol diets. *Xenobiotica* 16:531-542.

Brune, H., Deutsch-Wenzel, R.P., Habs, M., Ivankovic, S., and Schmahl, D. 1981. Investigation of the tumorigenic response to benzo(a)pyrene in aqueous caffeine solution applied orally to Sprague-Dawley rats. *J. Cancer Res. Clin. Oncol*. 102(2):153-157.

Burmaster, D.E. 1996. Using Beta Distributions Efficiently in a Probabilistic Exposure Assessment. Submitted to *Risk Analysis.*

Buchet, J.P., R. Lauwerys, and H. Roels. 1981a. Comparison of the Urinary Excretion of Arsenic Metabolites After a Single Oral Dose of Sodium Arsenite, Monomethylarsonate, or Dimethylarsinate in Man. Int Arch Occup Environ Health. (48):71-79.

Buchet, J.P., R. Lauwerys, and H. Roels. 1981b. Urinary Excretion of Inorganic Arsenic and Its Metabolites After Repeated Ingestion of Sodium Metaarsenite by Volunteers. Int Arch Occup Environ Health. (48):111-118.

CalEPA, 1994. California Cancer Potency Factors: Update. CalEPA Standards and Criteria Work Group. Office of Environmental Health Hazard Assessment. November 1.

Casteel, S.W., T, Evans, M.E. Dunsmore, C.P. Weis, B. Lavelle, W.J. Brattin, T.L. Hammon.

Relative bioavailability of arsenic in soils from the VBI170 site. Final Report. U.S. Environmental Protection Agency, Region 8, Denver, Co. (as cited in Roberts, et al. 2002).

Chang, L.H. 1943. The fecal excretion of Polycyclic Hydrocarbons Following Their Administration to the Rat. *J. Biol. Chem.* 151:93-99.

Chipman, J.K., Hirom, P.C., G.S. Frost, G.S., and Millburn, P. 1981a. The Biliary Excretion and Enterohepatic Circulation of Benzo(a)pyrene and its Metabolites in the Rat. *Biochemical Pharmacology* 30:937-944.

Chipman, J.K., Frost, G.S., Hirom, P.C., and Millburn, P. 1981b. Biliary excretion, systemic availability, and reactivity of metabolites following intraportal infusion of [3H]benzo[a]pyrene in the rat. *Carcinogenesis* 2:741-745.

Clinton, S.K. and Visek, W.J. 1988. Wheat Bran and the Induction of Intestinal Benzo(a) pyrene Hydroxylase by Dietary Benzo(a)pyrene. *J. Nutr.* 119:395-402.

Clonfero, E., Zordan, M., Cottica, D., Venier, P., Pozzoli, L., Cardin, E.L., Sarto, F., and Levis, A.G. 1986. Mutagenic activity and polycyclic aromatic hydrocarbon levels in urine of humans exposed to therapeutical coal tar. *Carcinogenesis* 7(5): 819-823.

Coulson, E.J., R.E. Remington and K.M. Lynch. 1935. Metabolism in the Rat of the Naturally Occurring Arsenic of Shrimp as Compared With Arsenic Trioxide. The Journal of Nutrition. (10):255-270.

Crecelius, E.A. 1977. Changes in the Chemical Speciation of Arsenic Following Ingestion by Man. Environmental Health Perspectives. (19):147-150.

Dankovic, D.A., Wright, C.W., Zangar, R.C., and Springer, D.L. 1989. Complex Mixture Effects on the Dermal Absorption of Benzo[a]pyrene and other Polycyclic Aromatic Hydrocarbons from Mouse Skin. *Journal of Applied Toxicology*, 9(4): 239-244.

Flescher, J.W. and Syndor, K.L. 1960. Distribution and Excretion of Radioactivity in Rats after Oral Administration of H3-3-Methylcholanthrene. *Proc. Soc. Expl. Biol. Med.* 104:776-779.

Foth, H., Kahl, R. and Hahl, G.F. 1988. Pharmacokinetics of low doses of benzo[a]pyrene in the rat. *Fd. Chem. Toxic.* 26:45-51.

Fries, G.F. and G.S. Marrow. 1975. Retention and excretion of 2,3,7,8-tetrachlorodibenzo-p- dioxin by rats. J. Agric. Food Chem. 23(2): 265-269.

Gregus, Z. and C.D. Klaassen. 1986. Disposition of Metals in Rats: A Comparative Study of Fecal, Urinary, and Biliary Excretion and Tissue Distribution of Eighteen Metals. Toxicol Appl Pharmacol. (85):24-38.

Grimmer, G., Brune, H., Dettbarn, G., Heinrich, U., Jacob, J., Mohtashamipur, E., Orpoth, K., Pott, F., and Wenzel-Hartung, R. 1988. Urinary and faecal excretion of

chrysene and chrysene metabolites by rats after oral, intreperitoneal, intratracheal or intrapulmonary application. *Arch. Toxicol.* 62:401-405.

Gulliver, W.P., Kutty, K.P., Laher, J.M., and Barrowman, J.A. 1983. In Vitro Interaction of 7,12- dimethylbenz[a]anthracene and its Biliary Metabolites with Dietary Fibers. *J. Nat. Cancer Inst.* 71:207-210.

Goon, D., N.S. Hatoum, J.D. Jernigan, S.L. Schmidt, and P.J. Garvin. 1990. Pharmacokinetics and Oral Bioavailability of Soil-Adsorbed Benzo(a)pyrene (B(a)P in Rats. *Toxicologist* 10:218.

Goon, D., N.S. Hatoum, M.J. Klan, J.D. Jerniganm and R.G. Farmer. 1991. Oral Bioavailability of "Aged" Soil-Adsorbed Benzo[a]pyrene (BaP) in Rats. *Toxicologist* 11:1356.

Goon, D. and Don Burnette. 1996. Personal Communication.

Gron, C., Oomen, A., Weyand, E., and Wittsiepe, J. 2007. Bioaccessibility of PAH from Danish soils. *Journal of Environmental Science and Health, Part A*. 42: 1233-1239.

Harrisson, J.W.E., E.W. Packman, and D.D. Abbott. 1956. Acute Oral Toxicity and Chemical and Physical Properties of Arsenic Trioxides. *A.M.A. Archives of Indistrial Health* 17:118-123.

Hecht, S.S., Grabowski, W. and Groth, K. 1979. Analysis of Feces for Benzo(a)pyrene After Consumption of Charcoal-Broiled Beef by Rats and Humans. *Cosmet. Toxicol*. 17:223-227.

Hindmarsh, J.T. and R.F. McCurdy. 1986. Clinical and Environmental Aspects of Arsenic Toxicity. *CRC Critical Reviews in Clinical Laboratory Sciences* 23(4):315-347.

Huq, A.S., Ho, N.F.H., Husari, N., Flynn, G.L., Jetzer, W.E., and Condie, L. 1986. Permeation of Water Contaminative Phenols Through Hairless Mouse Skin. *Arch. Environ. Contam. Toxicol.* 15:557-566.

Kao, J., Patterson, F.K., and Hall, J. 1985. Skin Penetration and Metabolism of Topically Applied Chemicals in Six Mammalian Species, Including Man: An In Vitro Study With Benzo(a)pyrene and Testosterone. *Toxicol. Appl. Pharmacol*. 81:502-516.

Kimbrough, R., H. Falk, P. Stehr, and G. Fries. 1985. Health implication of 2,3,7,8 - tetrachlorodibenzo(p)dioxin (TCDD) contamination of residential soil. J. Toxicol. Environ. Health 14:47-93.

Klaassen, C.D. 1974. Biliary Excretion of Arsenic in Rats, Rabbits, and Dogs. Toxicol Appl Pharmacol. (29):447-457.

Kociba, R.J., D.G. Keyes, J.E. Beyer, et al. 1978. Results of a two-year chronic toxicity and oncogenicity study of 2,3,7,8-tetrachlorodibenzo-p-dioxin in rats. Toxicol. Appl. Pharmacol. 46(2):279-303.

Koganti, A., Spina, D.A., Rozett, K. Ma, B-L., Weyand, E.H., Taylor, B.B., and Mauro, D.M. 1998. Studies on the applicability of biomarkers in estimating the systemic bioavailability of polynuclear aromatic hydrocarbons from manufactured gas plant tar-contaminated soils. *Environmental Science and Tecnology* (32):3104-3112.

Lucier, G.W., R.C. Rumbaugh, Z. McCoy, R. Hass, D. Harvan, and P. Albro. 1986. Ingestion of Soil Contaminated with 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) Alters Hepatic Enzyme Activites in Rats. *Fundamental and Applied Toxicology* 6:364-371.

Magee, B., Anderson, P. and Burmaster, P. 1996. Absorption Adjustment Factors (AAF) distriutions for Polycyclic Aromatic Hydrocarbons (PAH). *Human and Ecological Risk Assessment*. (2):841-873.

Magee, B.H., Dolan, D.G., Paley, D.A., and Weyand, E. 1999. Benzo[a]pyrene bioavailability from residential soils. *The Toxicologist* (48):11

McConnell, E., G. Lucier, R. Rumbaugh, P. Albro, D. Harvan, J. Hass and M. Harris. 1984. Dioxin in soil: bioavailability after ingestion by rats and guinea pigs. Science 223:1077-1079.

Mealey, J. Jr., G.L. Brownell, and W.H. Sweet. 1959. Radioarsenic in Plasma, Urine, Normal Tissues, and Intracranial Neoplasms: Distribution and Turnover after Intravenous Injection in Man. Am Med Assoc Arch Neurol Psychiat. (81):310-320.

Mirvish, S.S., Ghadirian, P., Wallcave, L., Raha, C., Bronczyk, S., and Sams, J.P. 1981. Effect of Diet on Fecal Excretion and Gastrointestinal Tract Distribution of Unmetabolized Benzo(a)pyrene and 3-Methylcholanthrene When These Compounds Are Administered Orally to Hamsters. *Cancer Research* 41:2289-2293.

Neal, J. and Rigdon, R.H. 1967. Gastric Tumors in Mice Fed Benzo(a)pyrene: A Quantitative Study. *Texas Rep. Biol. Med.* 25:553.

Ng, K.M.E., Chu, I., Bronaugh, R.L., Franklin, C.A., and Somers, D.A. 1992. Percutaneous Absorption and Metabolism of Pyrene, Benzo[a]pyrene, and Di(2-ethylhexyl) Phthalate: Comparison of *in Vitro* and *in Vivo* Results in the Hairless Guinea Pig. *Toxicology and Applied Pharmacology* 115: 216-223.

Ng, J.C., S.M. Kratzmann, L.Qi, H. Crawlwy, B. Chiswell, and M.R. Moore. 1998. Speciation and absolute bioavailability: risk assessment of arsenic-contaminated sites in a residential suburb in Canberra. *Analyst* 123:889-892.

Olson, J.R., T.A. Gasiewicz and R.A. Neal. 1980a. Tissue distribution, excretion, and metabolism of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) in the Golden Syrian hamster. Toxicol. Appl. Pharmacol. 56:78-85.

Piper, W.N., J.Q. Rose and P.J. Gehring. 1973. Excretion and Tissue Distribution of 2,3,7,8-Tetrachlorodibenzo-p-dioxin in the Rat. Environ. Health Perspect. Sept. (5):241-244.

Poiger, H. and C. Schlatter. 1980. Influence of Solvents and Absorbents on Dermal and Intestinal Absorption of TCDD. Food Cosmet. Toxicol. 18:477-481.

Poiger, H. and C. Schlatter. 1986. Pharmacokinetics of 2,3,7,8-TCDD in man. Chemosphere 15:1489-1494.

Pomroy, C., S.M. Charbonneau, R.S. McCullough and G.K.H. Tam. 1980. Human Retention Studies with ^{74}As. Toxicol Appl Pharmacol. (53):550-556.

Rabache, M.C. Billaud and Adrian, J. 1985. Evolution du benzo(a)pyrene dans le tube digestif. 1. Sa disparition. Internat. *J. Vit. Nutr. Res.* 55:113-117.

Rees, E.D., Mandelstam, P., Lowry, J.Q., and Lipscomb, H. 1971. A study of the mechanism of intestinal absorption of benzo(a)pyrene. *Biochemica et Biophysica Acta* 225:96-107.

Roberts, M.S., Anderson, R.A., and Swarbrick, J. 1977. Permeability of human epidermis to phenolic compounds. *Pharm. Pharmac.* 29:677-683.

Roberts, S.M., W.R. Weiman, J.R.T. Vinson, J.W. Munson and R.J. Bergeron. 2002. Measurement of Arsenic Bioavailability in Soil Using a Primate Model. *Toxicological Sciences* (67): 303-311.

Rose, J.Q., J.C. Ramsey, T.H. Wentzler, R.A. Humeland P.J. Gehring. 1976. The fate of 2,3,7,8-tetrachlorodibenzo-p-dioxin following single and repeated oral doses to the rat. Toxicol. Appl. Pharmacol. 36(2):209-226.

Roy, T.A., J.J. Yang, A.J. Krueger and C.R. Mackerer. 1990. Percutaneous Absorption of Neat 2,3,7,8-Tetrachloro-Dibenzo-p-Dioxin (TCDD) and TCDD Sorbed on Soils. Toxicologist 10:308.

Roy, T.A., Kruger, A.J. Taylor, B.B., Mauro, D.M., and Goldstein, L.S. 1998. Studies estimating the dermal bioavailability of polynuclear aromatic hydrocarbons from manufactured gas plant tar-contaminated soils. *Environmental Science and Technology* (32):3113-3117.

Ruby, M.V., R. Schoof, W. Brattin, M.Goldade, G. Post, M. Harnois, D.E. Mosby, S.W. Casteel, W. Berti, M. Carpenter, D. Edwards, D. Cragin, and W. Chappell. 1999. Advances in Evaluating the Oral Bioavaioability of Inorganics in Soil for Use in Human Health Risk Assessment. *EST* 33:3697-3705.

Sanders, C.L., Skinner, C., Gelman, R.A. 1984. Percutaneous Absorption of [7, 10^{-14} C] Benzo[a]Pyrene and [7,12-14C] Dimethylbenz[a]Anthracene in Mice. *Environmental Research* 33: 353-360.

Sato, T., Ose, Y., Nagase, H., and Hayase, K. 1987. Mechanism of the desmutagenic effect of humic acid. *Mutation Research* 176:199-204.

Schoket, B., Horkay, I., Kosa, A., Paldeak, L., Hewer, A., Grover, P.L., and Philips, D.H. 1990.Formation of DNA Adducts in the Skin of Psoriasis Patients, in Human Skin in

Organ Culture, and in Mouse Skin and Lung Following Topical Application of Coal-Tar and Juniper Tar. *Journal of Investigative Dermatology*. pp. 241-246.

Shu, H., D. Paustenbach, F.J. murray, L. Marple, B. Brunck, D. Dei Rossi, and P. Teitelbaum. 1988. Bioavailability of Soil-Bound TCDD: Oral Bioavailability in the Rat. *Fundamental and Applied Toxicology* 10:648-654.

Shu, H., P. Teitelbaum, A.S. Webb, et al. 1988. Bioavailability of Soil-Bound TCDD: Dermal Bioavailability in the Rat. *Fundamental and Applied Toxicology* 10:335-343.

Singh, R., Tucek, M., Maxa, K., Tenglerova, T., and Weyand, E.H. 1995. A Rapid and Simple Method for the Analysis of 1-hydroxypyrene glucuronide: A Potential Biomarker for Polycyclic Aromatic Hydrocarbon Exposure. *Carcinogenesis* 16:2909-2915.

Storer, J.S., DeLeon, I., Millikan, L.E., Laseter, J.L., and Griffing, C. 1984. Human Absorption of Crude Coal Tar Products. *Arch. Dermatol.* 120: 874-877.

Storm, J.E., Collier, S.W., Stewart, R.F., and Bronaugh, R.L. 1990. Metabolism of Xenobiotics during Percutaneous Penetration: Role of Absorption Rate and Cutaneous Enzyme Activity. *Fundamental and Applied Toxicology* 15: 132-141.

Thyssen, J., Althoff, H., Kimmerle, G., and Mohr, U. 1981. Inhalation studies with benzo(a)pyrene in Syrian golden hamsters. *J. Nat. Cancer Inst*. 66: 575-577.

Umbreit, T.H., E. J. hesse and M.A. Gallo. 1986. Bioavailability of Dioxin in Soil from a 2,4,5-T Manufacturing Site. *Science* 232:497-499.

Umbreit, T.H., E. J. Hesse, and M. A. Gallo. 1987. Differential Bioavailability of 2,3,7,8-Tetrachlorodibenzo-p-dioxin from Contaminated Soils. in Exner, J.H. (ed.) Solving Hazardous Waste Problems: Learning from Dioxins (American Chemical Society; Washington. D.C.).

U.S. EPA. 1985. Health Assessment Document for Polychlorinated Dibenzo-p-dioxin. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. EPA-600/8-84-014F. NTIS PB86-122546.

U.S. EPA. 1992a. Guidelines for Exposure Assessment. (Final). 57 *Federal Register* 22888-22938.

U.S. EPA. 1992b. Dermal Exposure Assessment Principles and Applications. Office of Research and Development. Washington, D.C. EPA 600/8-91/011B.

U.S. EPA. 1993. Provisional Guidance for Quantitative Risk Assessment of Polycyclic Aromatic Hydrocarbons. Office of Research and Development, Washington, D.C. EPA/600/R-93/089

U.S. EPA. 2001. Integrated Risk Information System (IRIS). Environmental Criteria and Assessment Office. Cincinnati, OH.

U.S. EPA. 2008. Integrated Risk Information System. On-Line Database.

Van den Berg, M., Olie, K., Hutzinger, O. 1983. Uptake and selective retention in rats of orally administered chlorinated dioxins and dibenzo-furans from fly-ash and fly-ash extract. *Chemosphere.* 12(4/5): 537-544.

VanRooij, J.G.M., Vinke, E., De Lange, J., Bruijnzeel, P.L.B., Bodelier-Bade, M.M., Noordhoek, J., and Jongeneelen, F.J. 1995. Dermal Absorption of Polycyclic Aromatic Hydrocarbons in the Blood-perfused Pig Ear. *Journal of Applied Toxicology* 15(3):193-200.

Wester, R.D., Maibach, H.I., Bucks, D.A., Sedik, L., Melendres, J., Liao, C., and DiZio, S. 1990. Percutaneous Absorption of [^{14}C]DDT and [^{14}C] Benzo(a)pyrene from Soil. *Fundam. Appl. Toxicol.* 15:510-516.

Wester, R.C., H. I. Maibach, L. Sedik, J. Melendres, and M. Wade. 1993. *In Vivo* and *In Vitro* Percutaneous Absorption and Skin Decontmination of Arsenic from Water and Soil. *Fundamental and Applied Toxicology* 20:336-340.

Weyand, E.H., Rozett, K., Koganti, A., and Singh, R. 1996. Effect of Soil on the Genotoxicity of Manufactured Gas Plant Residue. *Fundamental and Applied Toxicology* 30:1, Part 2.

Withey, J.R., Law, F.C.P., and Endrenyi, L. 1991. Pharmacokinetics and Bioavailability of Pyrene in the Rat. *J. Toxicol. Environ. Health* 32:429-447.

Wittsiepe, J., Erlenkamper, B., Welge, P., Hack, A., and Wilhelm, M. 2007. Bioavailability of PCDD/F from contaminated soil in young Goettingen minipigs. *Chemosphere*. 67: S355-S364.

World Health Organization (WHO). 1981. IARC Mongraphs on the Evaluation of the Carcinogenic Risk of Chemicals to Humans: Volume 25, Wood, Leather, and Associated Industries.

Yang, J.L., Roy, T.A., and Mackerer, C.R. 1986a. Percutaneous Absorption of Anthracene in the Rat: Comparison of *in vivo* and *in vitro* results. *Toxicology and Industrial Health*, 2(1): 79- 84.

Yang, J.L., Roy, T.A., and Mackerer, C.R. 1986b. Percutaneous Absorption of Benzo[a]Pyrene in the Rat: Comparison of *in vivo* and *in vitro* results. *Toxicology and Industrial Health*, Vol. 2, No. 4.

Yang, J.J., Roy, T.A., Krueger, A.J., Neil, W., and Mackerer, D.R. 1989. In Vitro and In Vivo Percutaneous Absorption of Benzo(a)pyrene From Petroleum Crude-Fortified Soil in the Rat. *Bull. Environ. Contam. Toxicol.* 43:207-214.