Appendix F

Dermal Exposure to Soil-Bound Hot Spots Multipathway Chemicals: Fractional Absorption (ABS) Values

F.1 Introduction

The absorbed dose resulting from dermal exposure to soil-bound chemicals depends on many factors. An algorithm that describes the uptake of chemicals from soil as a function of exposure duration, exposure frequency, chemical concentration in the soil, soil loading, surface area, body weight, averaging time, and fractional absorption (ABS) is discussed in Chapter 6. The purpose of this appendix is to summarize the derivation of the ABS for the "Hot Spots" multipathway chemicals and present the information used in the development of each chemical ABS. A general discussion of the diverse factors influencing dermal absorption of soil-bound chemicals is presented below preceding the chemical ABS summaries.

A small subset of organic and inorganic compounds evaluated under the Hot Spots program is subject to deposition onto soil, plants and water bodies. Therefore, exposure can occur by pathways other than inhalation. These chemicals are semi-volatile or nonvolatile, and are therefore partially or wholly in the solid or liquid phase after being emitted. Fate and transport of the deposited chemical must then be estimated in order to assess the impact on soil, water and foods that humans come in contact with. The basis for the selection of these compounds as "Hot Spots" multipathway substances can be found in Appendix E. The organic compounds of relevance listed under the "Hot Spots" program include 4,4'-methylene dianiline, hexachlorocyclohexanes, di(2-ethylhexyl)phthalate (DEHP), polychlorinated dibenzodioxins and dibenzofurans (PCDD/Fs), polychlorinated biphenyls (PCBs) and polycyclic aromatic hydrocarbons (PAHs). The inorganic metals and chemicals of relevance include the inorganic salts of arsenic, beryllium, cadmium, fluoride, mercury, lead, nickel, selenium and hexavalent chromium.

F.1.1 Point Estimate Approach for ABS Derivation

An ABS is a chemical-dependent, scenario-dependent value that can vary with the characteristics of the soil matrix and the exposed population. Such characteristics include the relative lipophilicity/hydrophilicity of the compound, soil organic content, soil particle size, soil aging of the chemical, residence time on the skin, and exposed surface area. Some of these issues are discussed in greater detail in Chapter 6. The data necessary to characterize the variability in these variates are often not available. For this reason, the ABS values derived in this document are point estimates. In particular, site specific information on soil organic content and soil particle range are not available. These factors can have

a significant impact on chemical absorption from soil, and the uncertainty in the dose estimate from dermal absorption because of these and other factors can be large.

To derive a point estimate for a chemical, typically the value from the best and sometimes only study available was selected. If multiple studies were available with data collected under similar conditions, the most comprehensive study was selected. Or if the studies were of equal reliability, their absorption values would be averaged for ABS determination. In some cases experimental data are not sufficient for a point estimate ABS and a default ABS is recommended (see below).

F.1.2 Skin Morphology and Dermal Absorption Issues for ABS Determination

The transepidermal uptake of chemicals across skin involves a complex process of transport from the soil matrix to the external protective skin layer called the epidermis, and then through the epidermis to the underlying dermis. The outermost layer of the epidermis is called the stratum corneum, which is thought to provide the major barrier to the absorption of most substances deposited onto the skin surface. The stratum corneum in humans varies in thickness from about 5 µm to over 400 µm on the palms and soles of the feet (Poet and McDougal, 2002; Hostynek, 2003). Below lies the viable epidermis, about 50-100 µm thick, containing keratinocytes that proliferate and differentiate while moving upwards and replacing the stratum corneum cells as they wear away. Below the epidermis lies the hydrous tissue of the dermis perfused by the blood and lymphatic circulation.

Skin appendages, including hair follicles and sweat ducts, transit through all these layers and may provide an alternate pathway for dermal diffusion of some ions such as metal salts (Tregear, 1966; Flynn, 1990). However, skin appendages occupy only a fraction of the surface area of the skin, which may limit their potential as a major diffusion pathway into the systemic circulation.

During the transport through the viable-epidermal and dermal layers, metabolism may also play a role in the absorption process (Kao and Carver, 1990). Metabolism in the dermal layers could also activate a toxicant, resulting in skin as a target organ or producing toxicity elsewhere following systemic absorption. As noted above, specific dermal ABS values for soil-bound chemicals are difficult to obtain due in part to the complex multiphasic nature of the system and lack of published absorption data. Hawley (1985) suggested a default factor of 15 percent to correct for the effect of the soil matrix on the dermal uptake of organic chemicals. Experimental evidence, however, suggests absorption from soil will be chemical dependent. Hence, it is important to determine dermal uptake point estimate values for specific soil-bound chemicals where appropriate data are available, as they will be more accurate than those derived on broad-based assumptions.

To obtain the ABS, a measured amount of chemical in a given amount of soil is administered to the skin surface; this amount (wt chemical/area skin) is referred to as the applied dose. The amount of chemical that crosses the skin barrier is measured and the ABS is calculated by dividing the amount absorbed by the amount applied. When measurements are made in excreta or specific organs, corrections are included for incomplete recovery. In experiments of this type, the administered amount (in soil or solvent) represents a finite level of application. The ABS so calculated is an experimental value that is dependent upon exposure conditions, such as length of exposure and extent of soil loading. The length of exposure used for dermal exposure assessment in this document is 24 hrs. A 24 hr exposure time is commonly used in dermal absorption studies, so it's compatible for ABS calculation. In instances where absorption data did not use 24 hr exposure, an ABS will generally be based on data that are nearest to 24 hr exposure.

In contrast to the studies that utilize the application of finite amounts of chemicals, dermal studies that mimic scenarios such as bathing and swimming, require the applications of infinite volumes, i.e. the volume of the administered dose is much larger than the volume of the exposed skin area and the chemical at the skin surface is continuously replenished. The latter exposure scenario is not applicable to the soil studies described in this chapter, although information obtained from such studies may be useful for discussion purposes. For additional information on dermal uptake of chemicals from water (or vapor), the reader is referred to U.S. EPA (2004). The dermal absorption of chemicals from dermal exposure to contaminated water is not addressed in the "Hot Spots" program because it is likely to be a minor contribution to overall dose if it occurs at all.

F.2 Risk Assessment Issues

Although all dermal absorption studies are useful for understanding the relationship between dermal exposure and absorption, the application of these studies to risk assessment involves specific issues that must be considered to avoid development of a point estimate that may greatly underestimate, or overestimate, the potential for dermal absorption. Included among these issues are biological characteristics, soil properties, and exposure scenarios, and the variability in each can introduce uncertainties into the point estimate determination of ABS. By understanding these issues, the implications of using experimentally derived dermal ABS can be better understood. Specific categories of issues that must be considered when assessing dermal absorption are discussed below.

F.2.1 Definition of Dermal Uptake

Comprehensive dermal absorption studies often include a quantitative analysis of the amount of chemical that has passed through skin into the systemic circulation (for in vivo studies) or appears in the receptor fluid (for in vitro studies), plus the

amount of chemical remaining in the skin at the site of application. Fundamentally, dermal uptake/absorption refers to the amount of dermally applied chemical that is ultimately determined to be systemically available. Because absorbed chemicals may be retained in the skin for long periods of time and act as a reservoir for the slow systemic absorption of chemicals, the chemical remaining in skin at the end of dermal absorption experiments is considered available for systemic absorption unless data are available that shows otherwise.

Some fraction of dermally-absorbed chemicals may be only superficially diffused into skin and deposit in the stratum corneum where they are subject to counter-current forces of skin shedding, or desquamation, and ultimately removed from the body before becoming systemically absorbed. Continuous desquamation with total stratum corneum turnover has been estimated to take 2-3 weeks (Hostynek, 2003). Modeling calculations by Reddy et al. (2000) indicate that epidermal turnover can significantly reduce subsequent chemical absorption into the systemic circulation for highly lipophilic (log K_{ow} > about 4) or high molecular weight chemicals (MW > about 350-400 Da). However, some highly lipophilic chemicals retained in skin at the end of dermal absorption studies have been shown to be predominantly available for eventual absorption into the systemic circulation. Multipathway Hot Spots chemicals that fall into this category include the PAHs and DEHP (Chu et al., 1996).

Loss of absorbed chemical through skin shedding appears to occur more readily with some hydrophilic metal salts in which a portion of the metal becomes irreversibly bound in the epidermis and subject to eventual shedding with skin. Some metal salts have such a slow diffusion (i.e., long lag time) through skin that the stratum corneum turnover rate exceeds the chemical diffusion rate (Hostynek, 2003).

Tape stripping methods to remove thin layers of stratum corneum have been used in several studies discussed below to estimate the fraction of chemical in the stratum corneum that may be lost through desquamation. A more definitive approach used in a few cases is to extend the dermal uptake study for an additional few days (after excess chemical is removed from the skin surface) to determine if more of the chemical retained in the skin becomes available for systemic absorption. Other studies that help determine the fate of chemicals retained in skin include skin localization techniques and skin binding studies (Miselnicky et al., 1988; Yourick et al., 2004). But in many instances the dermal uptake studies for individual chemicals did not provide enough data to determine the fate or location of the chemical retained in skin. Thus, as discussed above, the ABS will then represent that fraction of chemical still retained in skin, plus the fraction that has already passed through the skin.

F.2.2 Dermal Bioavailability of Chemicals in Soil

The term dermal bioavailability as it applies in this section refers to the fraction of chemical in soil that is actually dermally absorbed. Dermal bioaccessibility is another term used in reference to chemical-laden soils and represents that fraction of chemical solubilized from soil, usually into water, sweat, or gastrointestinal fluids that then becomes available for absorption. By definition, bioaccessibility should exceed bioavailability.

Published data for some chemicals considered in this section contain only data for neat application of the chemical to skin in solvent or aqueous vehicle. Generally, there is a lack of absorption data for chemicals bound to soil. To avoid potential overestimation of absorption in these instances, bioaccessibility and soil leaching studies of soil-bound chemicals are considered for adjusting the fractional absorption of the pure chemical applied to skin. These studies can be used to determine the extractable, or bioaccessible, fraction of a soil pollutant that can be deposited on the skin surface. Water added to soil is often used to determine the bioaccessibility of a soil-bound chemical, although human sweat or synthetic sweat has also been used to estimate the amount of a pollutant that can be leached from contaminated soils (Horowitz and Finley, 1993; Filon et al., 2006; Nico et al., 2006).

F.2.3 Soil - Chemical - Tissue Interaction.

Soil is a complex matrix with a highly variable composition and absorptive capacity. Organic content, mineral composition, particle size, and pH are all highly variable. Because the dermal absorption of a compound from soil is often dependent on these characteristics, it follows that transfer of a chemical from soil particles to the skin surface for absorption is likely to vary with soil type.

Transfer of a chemical from soil particles to the skin surface is limited by the chemical's diffusion rate (McKone, 1990). Diffusion through the soil phase, through the air, and through soil moisture is all possible. Fugacity-based interphase transport models were constructed to describe the rate of each of these processes for chemicals in soil particles and to predict the dermal uptake rates. It was shown that predicted dermal uptake of chemicals from soil depends on the Henry's constant (vapor pressure/solubility in water), the octanol/water partition coefficient of a chemical, and the soil thickness on skin. If the Henry's constant is very high, chemicals will be lost from soil particles (or the skin surface) quite rapidly, so net dermal uptake of chemicals added to soil will be low. If the Henry's constant is very low, diffusion through the soil particle layer will be too slow to allow much dermal uptake unless the soil particles are very small. A high octanol/water partition coefficient is associated with tight binding to soil and low water solubility; these properties also limit the ability of a chemical to diffuse through the mixed lipid/water phases of the stratum corneum.

Other mathematical models have been developed by Bunge and Parks (1997) to describe dermal absorption of organic chemicals provided the chemical fits certain assumptions, such as falling within a defined octanol/water partition coefficient range ($1.59 \leq \log_{10}K_{ow} \leq 5.53$), and that the molecular weight of the organic chemical is ≤ 700. Soil constraints for the model include contaminated soils with about 0.2% organic carbon or more, and with a clay fraction less than 60 times the weight fraction of organic carbon. The models were then used to estimate the relative effect of changing exposure conditions (e.g., changes in soil loading, contamination levels, chemical, etc.) compared to published experimental studies. Although the models were generally consistent with the experimental results for some chemicals, such as benzo(a)pyrene (BaP), they were considerably divergent from the experimental results for other chemicals, such as lindane (gamma-hexachlorocyclohexane).

The authors suggested that the fast soil release kinetics on which the models are based may not fit with what was observed experimentally for some chemicals (Bunge and Parks, 1997). Fast soil release kinetics assumes the primary resistance that controls transfer of the chemical from soil to skin resides in the dermal barrier, and that the kinetics of soil desorption are relatively insignificant. Lindane may exhibit slow soil release characteristics in various soils (i.e., soil desorption of the chemical is the controlling influence for dermal absorption), which limits the amount of dermal absorption predicted by the models.

Alternatively, Shatkin et al. (2002) developed a two-stage fugacity-based model specifically for BaP that incorporated both a fast soil desorption phase and a slow desorption phase of BaP from soil. Based on the several parameters investigated that would affect dermal bioavailability, the authors predicted that the fast desorption kinetics of a soil had a greater impact on predicted dermal uptake than any other parameter, including organic carbon content of a soil.

These examples show that the effect of soil on the dermal uptake of organic compounds can be difficult to predict without experimental data. However, dermal absorption by metal salts can be expected to be a more complex process than dermal absorption of organic compounds. Factors affecting absorption of soil-bound metals include pH, metal oxidation state, counter ion, size and solubility (Hostynek, 2003). For example, lead becomes more soluble and available for uptake in soil at low pH. However, a low soil pH tends to convert chromium (VI) to the larger less permeable chromium (III) ion. This reduction in chromium valence can also occur in transit through the skin and considerably slow the absorption of chromium through skin.

F.2.4 Effect of Soil Organic Content on Dermal Absorption

For the soil pollutants discussed in this section, one of the most common soil variables explored for effect on dermal absorption of a chemical is the organic carbon or organic matter content. The chemical adsorbed to the organic carbon phase will generally be less available for transfer to skin than neat chemical

present in a separate liquid phase in the soil, largely due to strong adsorption of the chemical to the organic carbon fraction (Bunge and Parks, 1996). Dermal bioavailability of a chemical in soil also tends to decrease with increasing organic carbon content of the soil (Sheppard and Evenden, 1994; Bunge and Parks, 1997). Consequently, a number of studies compared the effect of varying the soil organic content on the dermal absorption of a chemical. The health protective approach for estimating an ABS would be to base the value on the higher dermal absorption from these studies, often from the soil with lower organic carbon content.

The length of time required for a chemical to partition to the soil organic material may be quite short (a few days) or longer (more than a month), depending on the nature of the deposited chemical, the soil and the weather (Bunge and Parks, 1996). However, early dermal absorption studies of chemicals in soil were usually conducted with freshly spiked soil just prior to exposure. Regardless of the partitioning time to the soil organic carbon, addition of a chemical to soil can often result in a reduction of dermal bioavailability relative to the pure chemical. For a group of selected organic compounds (e.g., DDT, BaP, PCBs, etc.) and arsenic, addition to soil just before loading onto skin reduced the overall dermal uptake by an average of about 60% compared to dermal uptake of the pure chemical (Wester and Maibach, 1999). However, a reduction in absorption from soil relative to a neat solution cannot be predicted for all chemicals. Dermal absorption for some chemicals such as arsenic in soil was found to be essentially unchanged compared to absorption from the neat solution.

F.2.5 Soil Aging Effects

The ABS point estimates presented here are primarily based on soils that were freshly spiked with contaminants and placed on skin for roughly 24 hrs. As such, the ABS point estimates largely represent the initial fast phase of decreased bioavailability when a chemical is freshly added to soil prior to skin exposure (Alexander, 1995; Bunge and Parks, 1997). This phase is generally a reversible process, such that a chemical sorbed to soil may become desorbed and be available for uptake during the skin exposure.

However, over time many chemicals added to soil undergo a slower second phase of decreased bioavailability. The soil-deposited chemicals tend to move from the external surface of soil particles to internal and more remote sites within the soil matrix so that chemicals become increasingly more desorption-resistant, a process known as aging (Alexander, 1995). A number of recent dermal absorption studies discussed below have observed reductions in dermal absorption occurring for up to 3-6 months following addition of the chemical to soil. Reductions of about 50% have been observed for dermal absorption of BaP aged in soil compared to soils freshly spiked prior to skin application (Roy and Singh, 2001). Abdel-Rahman et al. (1999) observed up to a 7.5-fold reduction in dermal absorption for arsenic aged in soil.

The continuous input of chemicals deposited on soils in the vicinity of "Hot Spots" stationary sources will likely result in the less recently deposited chemicals undergoing soil aging. For toxic inorganic metals in soil, the dermal dose equation (Eq. 6.1) does not account for decreased bioaccessibility over time due to soil aging. Leaching and weathering effects are assumed to be very long (i.e., 10^8 days), unless site-specific information shows otherwise. Only a few studies have investigated the decrease in dermal absorption for specific inorganic metals and semi-metals aged in soils, including arsenic, nickel and mercury. The soil aging results from these studies are considered in the development of the ABS, although the volume of literature available is sparse. Therefore, dermal fractional absorption still relies primarily on data for freshly applied metals to soil to avoid underestimation of the ABS.

For organic chemicals, the soil half-life variable in Eq. 6.2 will account to some degree for the effects of soil aging, depending on the rigor of the extraction process used (Abdel-Rahman et al., 2002). Use of a strong acid extraction method may solubilize some of the desorption-resistant chemical from soil and overestimate the dermal bioaccessibility of a soil-aged organic chemical. That is why milder extraction methods have been recommended, such as soil extraction in synthetic sweat, to obtain a more applicable estimate of soil half-life.

F.2.6 Dermal Soil Loading and Adherence Characteristics

The ABS from soil depends on the amount of soil in contact with the skin. Maximal fractional absorption of a soil-bound chemical occurs when a monolayer of soil covers the skin (monolayer threshold). A monolayer can be defined, in this case, as a layer of soil on the skin equal in thickness to the average soil particle diameter. Theoretical calculations and experimental data show that increased soil loading (mg soil/cm^2 skin) beyond monolayer coverage usually leads to decreased fractional absorption as a result of some of the soil not being in direct contact with skin (McKone, 1990; Duff and Kissel, 1996; Bunge and Parks, 1997). Soil loading at which the monolayer exists depends on the soil particle size (Duff and Kissel, 1996). For example, sand with an average particle diameter of 0.044 cm reaches monolayer coverage at 61 mg/cm^2, whereas monolayer coverage with clay at a particle diameter of 0.0092 cm is 13 mg/cm^2 (USEPA, 2004).

Early soil loading experiments were carried out under conditions of high loading, e.g. 20-40 mg/cm^2 (Shu et al., 1988; Wester et al., 1990a; Wester et al., 1992) , without estimating monolayer coverage or providing average soil particle diameter to estimate monolayer coverage. High soil loadings that are greater than monolayer coverage may underestimate the fraction of chemical absorbed from soil. Coarse grain size (180 to 300 µm) used under the high loading conditions of 20-40 mg/cm^2 was at, or only, slightly more than monolayer coverage (Duff and Kissel, 1996). However, using such soil loadings with soils sieved to <150 µm would result in greater than monolayer coverage.

Typical soil loadings under most human exposure scenarios generally ranged from 0.01 to 0.2 mg/cm^2 when averaged over the entire exposed skin surface (USEPA, 2004). Soil loadings on the hands, the skin region with the highest soil loading, averaged about 1 to 5 mg/cm^2 during typical human activities in wet soil with a moisture content of 9 to 18%, and usually less than 0.1 mg/cm^2 with activities in dry soil with a moisture content of 3-4% (Kissel et al., 1998).

During dermal absorption studies, the soil used to measure dermal uptake is applied to the skin as a "dry" formulation, i.e. the solvent used in the preparation of the chemical laden soil is allowed to evaporate prior to dermal application. The uptake of a soil-bound chemical from wet soil is expected to exceed the uptake from dry soil because of the increased humidity and temperature at the skin surface (Wester and Maibach, 1983). Such conditions exist for human exposure scenarios that involve high humidity, high temperature, and skin covering (e.g. gloves and clothing). Some studies are carried out under condition of occluded skin, and these studies could be used to estimate chemical absorption from soil when moisture is present.

In addition, the particle size distribution of soil adhering to skin also needs to be considered in dermal absorption studies. Most recent dermal absorption studies have sieved soil down to <150 µm prior to spiking with chemical and applying to skin. Studies have shown that soil particles in this size range tend to adhere to skin to the greatest extent (Driver et al., 1989; Sheppard and Evenden, 1994; Kissel et al., 1996). In hand press studies by Kissel et al. (1996), small particles $\leq$150 µm were found to adhere preferentially over larger particles $\geq$250 µm in dry soils of <2% moisture. Adherence in wet soils (12-18%) was roughly proportional to the soil particle size distribution of the original soil, although no consistent adherence was seen with soil moisture and particle size with five soils studied. Monolayer coverage with soil sieved to <150 µm will vary depending on the particle characteristics, but was shown in one instance to be about 2 mg/cm^2 with an estimated mean grain size of 12 µm (Duff and Kissel, 1996).

Choate et al. (2006) found that the dermally adhered fractions of two soil samples with wide distributions of particle sizes generally consisted of particles of diameters <63 µm or <125 µm, depending on the soil sampled. Adherence was similar whether the soils were applied dry (1.58-1.85% moisture) or moderately moist (3.35-3.81% moisture). With increasing moisture content of roughly 10% or greater, adherence increases significantly and a greater proportion of larger soil particles >150 µm are represented in the adhered soil (Holmes et al., 1996; Kissel et al., 1996; Choate et al., 2006). Smaller adhering soil particles can be considerably different in composition, especially in organic carbon content, from larger particles that tend to stick to skin in less abundance. However, organic carbon content does not appear to enhance the adherence of any particle sizes (Holmes et al., 1996; Choate et al., 2006).

In a few cases, no dermal absorption data were available for a chemical mixed with soil. Therefore, ABS values were estimated from studies that applied the

chemical directly onto the skin. Kissel (2011) observed that fractional absorption of chemicals applied neat to skin are not generally independent of skin loading conditions. For example, the ABS will decrease as an organic chemical is increasingly loaded onto skin. In other words, absorption of an organic chemical through skin is flux-limited, and loading more chemical onto skin in a defined area will not increase flux, but will decrease the ABS value.

To aid interpretation of dermal absorption-related phenomena, Kissel (2011) proposed a dimensionless variate representing the ratio of mass delivery to plausible absorptive flux under experimental or environmental conditions. High values of this dimensionless dermal variate connote surplus supply (i.e., flux-limited) conditions. This situation is similar to loading skin with chemical-bound soil above monolayer levels. The potential mismeasure of dermal absorption with chemicals applied neat to skin is addressed below for every chemical in which an ABS is derived in this way.

F.2.7 In Vivo Vs. In Vitro Experiments

It is generally recognized that the most reliable method for assessing skin absorption of a chemical is to measure penetration in vivo using the appropriate animal model or human volunteers (Kao, 1990). Thus, in vivo data are preferred over in vitro data for determination of a chemical ABS in this exposure assessment. In vivo data may be lacking for some chemicals of interest in this document due to economic considerations for conducting tests in humans and other mammalian species, or due to ethical concerns for testing in humans.

In vitro studies have the benefit of measuring dermal absorption under more easily controlled environments. Human skin can be tested without the inherent risks of a clinical study, and absorption through skin and retention in skin can be directly measured. Consequently, in vitro dermal absorption studies are frequently performed and provide the basis for an ABS for some chemicals presented in this section, following careful consideration for relevance to in vivo human exposure.

Although good agreement has been found when comparing in vivo and in vitro absorption results for some chemicals, trends towards lower absorption with in vitro exposure have been observed. For example, lipophilic compounds frequently have limited solubility in the buffered aqueous receptor fluids often used for in vitro cell systems, impeding the flow into the receptor fluid and resulting in an underestimation of skin penetration (Wester and Maibach, 1999). In vivo, lipophilic compounds penetrate the stratum corneum and diffuse through skin and, because of the solubilizing and emulsifying abilities of biological fluid, may readily be taken away by the blood in the dermal vasculature.

A reduction in skin viability of excised skin samples may occur due to storage conditions prior to use and may affect dermal absorption measurements. For example, the metabolic properties of human skin are reduced if the skin samples

were previously frozen. Some polycyclic aromatic compounds (PAHs) undergo extensive percutaneous metabolism when absorbed, and reducing the metabolic capabilities of skin samples will reduce dermal penetration of absorbed PAHs (Kao et al., 1985; Ng et al., 1992; Moody et al., 2009a).

For metal salts, it has been postulated that low diffusion values through the stratum corneum in vitro are a result of skin shunts (e.g., hair follicles and sweat ducts) swelling shut upon hydration of skin samples (Tregear, 1966; Hostynek, 2003). Skin shunts that bypass the stratum corneum are thought by some to be a significant absorption route for charged metals. For example, dermal absorption of nickel salts shows there is a surge in diffusion at the earliest stage, which then rapidly decreases towards steady state (Tanojo et al., 2001). The decrease in diffusion rate has been proposed to be a result of the skin tissue becoming hydrated, shutting down the skin shunts.

A further potential limitation under in vitro conditions is that diffusing compounds must traverse the epidermis and the entire dermis in order to reach the receptor fluid. In vivo, the majority of the absorption into the cutaneous microcirculation is thought to occur in the upper dermis and the penetrant compounds may not have to diffuse across the entire thickness of the dermis. However, the bulk of the connective tissue in the dermis is often eliminated from the skin preparation by cutting the skin parallel to the skin surface with a dermatome (Poet and McDougal, 2002).

In vivo studies are not without limitations. Dermally applied chemicals are often radiolabeled to facilitate quantification of the usually low absolute amounts of chemical dermally absorbed. In small mammals, a total accounting of all dermally absorbed radioactivity can be estimated from excreta, carcass, and site of skin absorption. However, in larger mammals measurements of radiotracer are quantified in excreta and measurements from intravenous, intramuscular, or oral dosing are applied as a correction for tissue absorbed chemical. The validity of this method depends on the underlying assumption that metabolism and disposition of the applied compound is route independent, and that the pharmacokinetic behavior of the intravenous and topical doses is similar (Kao, 1990).

F.2.8 Inter- and Intra-Species Specificity

The variability in dermal absorption of chemicals among mammalian species has been investigated in vivo and in vitro. Bartek et al. (1972) suggest that the extent of in vivo uptake among animals follows the rank: rabbit > rat > pig ≈ monkey ≈ humans, based on dermal absorption of benzoic acid, hydrocortisone, testosterone, caffeine, N-acetylcysteine, and butter yellow. However, the species ranking did not strictly hold for all chemicals, indicating not only species-specific differences but also chemical-specific differences.

Comparison of data from other studies does support that in general, the absorption in the rabbit, rat and other rodents can considerably overestimate absorption in humans, while absorption in monkeys and miniature pigs most closely predict human absorption (Wester and Maibach, 1975; Reifenrath et al., 1984; Wester and Maibach, 1985; Bronaugh et al., 1990; Wester et al., 1998a). Alternatively, Kao et al. (1985) found that in vitro permeation of testosterone and BaP through human skin was greater than that for guinea pig, rat, or rabbit, indicating that species-specificity differences likely depend on other factors such as experimental conditions and tissue viability. Variability in dermal absorption depending on the skin area exposed has been investigated (Wester and Maibach, 1983). In humans, absorption across the skin varies by area of the body and may be higher than the commonly used forearm (e.g. scalp, axilla, forehead, jaw angle and scrotum).

F.2.9 Metabolism of Absorbed Chemicals in the Skin

The description of percutaneous absorption is generally based on diffusion models that take into account the physico-chemical characteristics of chemicals and soils. While such descriptions may help to explain the uptake of chemicals across the stratum corneum, the role played by metabolism in the viable epidermal and dermal layers should be included to understand the complete permeation of chemicals through the skin (Wester and Maibach, 1983; Kao and Carver, 1990; Bronaugh et al., 1994).

Viability of the skin refers to the status of active energy turnover, i.e. the utilization of glucose and formation of CO_2 or lactate in skin. Enzymes and metabolic processes in skin may affect the dermal penetration of drugs and other xenobiotics, particularly if absorbed chemicals can be metabolized in the skin. Using production of lactose as the measure of viability, human skin placed in a buffered solution and kept refrigerated remained viable for about 8 days following donor death (Wester et al., 1998b). Skin frozen for storage or heat-treated to separate the epidermis and dermis renders the skin non-viable and may change the dermal penetration dynamics of absorbed chemicals. Some early studies investigating the dermal penetration of chemicals used previously frozen skin samples and may not provide a good basis for ABS determination.

Dermal metabolism of BaP was observed to be considerably reduced in several mammalian species with use of non-viable skin, resulting in reduced penetration of BaP through skin (Kao et al., 1985). In viable human skin, nearly half the BaP that permeated the skin was attributed to BaP metabolites. In non-viable skin, essentially only unchanged BaP was detected in the receptor fluid. In fact, dermal absorption of polycyclic aromatic hydrocarbons (PAH) that include BaP resulted in PAH-DNA adducts in human skin samples, demonstrating that skin is a target organ due to metabolic activation of PAHs in skin (Phillips et al., 1990).

On the other hand, dermal absorption of some chemicals does not appear to be affected by the viability status of the skin samples. Dermal penetration of TCDD through viable and non-viable pig skin was found to be similar (Weber, 1993).

F.2.10 Human Adult and Infant Variability in Skin Permeability

Animal studies are designed to ensure uniformity within the experimental population by using inbred strains and often only one sex. The variability between animals is much less than the genetically diverse human population. Human studies also rarely use children or infants, the elderly, pregnant women and the infirm, partially because of ethical considerations. Dermal uptake may vary due to genetic diversity in the human population and differences in age. This variability will not necessarily be accounted for by experimental data.

A review of the data on human skin permeability to chemicals suggest at least a mean intra-individual coefficient of variation of approximately 40% and a mean inter-individual variation of about 70% (Loth et al., 2000; Hostynek, 2003). A leading cause in the variation is the lipid composition of the stratum corneum, which influences solubility and permeability of drugs. This factor is partly responsible for the high variability in accumulation and permeation measurements (Loth et al., 2000).

There has been increasing awareness in recent years that infants and children are more susceptible than adults to the harmful effects of some pollutants. This can be due to differences in exposure, physiology, absorption, distribution, metabolism, and excretion. Further, organ development and faster cell division influence targets of toxicity. Finally, a large skin surface area to body weight ratio would increase the dose of an absorbed chemical on a mg/kg body weight basis.

Only a few studies have examined age-related differences in the dermal absorption capacity of chemicals in infants and children compared to adults. Preterm infants lack a fully developed dermal barrier function and are particularly prone to accidental poisoning of toxic agents applied to the skin surface (Barrett and Rutter, 1994). In an in vitro system, McCormack et al. (1982) observed increased penetration of some alcohols and fatty acids through skin of premature infants compared to full term infant skin and adult skin. Dermal absorption of sodium salicylate was found to be a hundred- to a thousand-fold greater in infants of 30 weeks gestation or less compared to full term infants (Barker et al., 1987).

In full-term infants, epidermal structure and function matures by 2-3 weeks of age (Holbrook, 1998; Makri et al., 2004). In general, the in vitro system of McCormack et al. (1982) showed full-term baby skin to be a good barrier for some compounds. No difference in penetration of alcohols through full term infant and adult skin was seen. However, penetration of some fatty acids through full term infant skin was greater than that through adult skin. Higher lipid content in the stratum corneum of infants was thought to be the reason for

increased absorption of fatty acids. In addition, a layer of subcutaneous fat develops at approximately 2-3 months of age in infants and continues to exist through the early toddler period (Thompson, 1946; Banks et al., 1990; Cohen Hubal et al., 2000). This layer of fat may act as a sink for lipophilic chemicals absorbed through the skin.

Age-related changes in dermal absorption have also been investigated in experimental animal models. Using TCDD or 2,3,4,7,8-pentachlorodibenzo-p-dioxin (4-PeCDD) in solvent, Banks et al. (1990) observed greater absorption of TCDD or 4-PeCDD in 10-week old rats than 36 - 120-week old rats. 2,4,5,2',4',5'-Hexachlorobiphenyl showed significantly higher fractional penetration in young rats (33 days old) compared to adult rats (82 days old) in vivo, but only at one of three dose levels tested (Shah et al., 1987). Overall, the authors concluded that no clear age-related pattern of dermal absorption was found among a total of 14 pesticides including 2,4,5,2',4',5'-hexachlorobiphenyl.

F.2.11 Use of Default ABS Values

The California South Coast Air Quality Management District's Multi-Pathway Health Risk Assessment Input Parameters Guidance Document (SCAQMD, 1988) recommended using default values of 10% for organic chemicals and 1% for inorganic chemicals when quantitative data are not available to estimate chemical-specific dermal absorption fractions from soil.

Use of these default factors was proposed based on a review of the dermal absorption literature and recommendations by McLaughlin (1984). In his US EPA report, McLaughlin suggests it may be possible to group penetrants into a numerical system using an "order of magnitude" approach (i.e., 100% - 10% - 1% - 0.1% fractional absorption groupings), depending on physical parameters such as partition coefficients and diffusion constants. For example, many of the organic compounds were found to fall into the 10% absorption range. Exceptions included some pesticides, such as the very lipophilic pesticide carbaryl that exhibited a fractional absorption closer to 100%, and the polar pesticide diquat that exhibited a fractional absorption closer to 1%.

More recently, US EPA (2004) also recommended a default dermal absorption fraction for semivolatile organic compounds (SVOCs) of 10% as a screening method for the majority of SVOCs without dermal absorption values. This fraction was suggested because the experimental values for SVOCs determined by US EPA are assumed to be representative of all SVOCs as a class. US EPA (2004) notes that chemicals within classes can vary widely in structure and chemical properties, potentially resulting in a wide range of fractional absorption values. However, OEHHA agrees that a 10% fractional absorption default value is acceptable at this time, based on the range of values (3 to 14%) estimated in Table F.5 for SVOCs. Currently, the OEHHA default ABS value for organic compounds applies only to 4,4'-methylene dianiline.

For inorganic classes of compounds, US EPA (2004) recommended that no default dermal absorption values be used. The premise was that speciation of inorganic compounds is critical to the dermal absorption and there are too little data to extrapolate a reasonable default value. OEHHA notes that the range of ABS point estimate values for the metal and semi-metal salts (see Table F.5) is between 0.2 and 6%. Therefore, it is reasonable to assume that a default ABS of 3% can be used as a screening value, based on the mean ABS value for the metals and semi-metals in which published dermal absorption data exists (i.e., arsenic, cadmium, hexavalent chromium, lead, mercury and nickel). Currently, the default ABS value for inorganic compounds applies only to fluoride, beryllium and selenium.

F.3 Point Estimates for Dermal Absorption (ABS) of Inorganic Compounds

F.3.1 Arsenic and Arsenic Compounds

Recommended point estimate for dermal uptake: 6%

F.3.1.1 Studies Considered

A. Key Studies

Wester et al. (1993a) examined the in vivo percutaneous absorption of radiolabeled soluble arsenic (as $H_3{}^{73}AsO_4$) freshly mixed with soil and applied to skin of female Rhesus monkeys (n = 4 animals per dose group). Dose levels of 0.0004 and 0.6 $\mu g/cm^2$ were used. The soil load on the skin was 40 mg soil/cm^2 skin area. The soil had been sieved to 180-300 µm prior to application, thus, a soil load of 40 mg/cm^2 was likely at or near monolayer coverage. Topical doses were applied to an area of the abdomen for 24 hours. Urine was collected during the dosing period, and through the following 6 days. For comparison, radiolabeled arsenic (as ^{73}As) in water was administered intravenously to four monkeys. Percutaneous absorption was determined by the ratio of urinary arsenic excretion following topical application to that following intravenous administration.

Urinary excretion of the ^{73}As label was complete by day 7, with about half the label excreted in the first 24-48 hrs following topical administration. Results of this study showed that the percutaneous absorption of arsenic from soil was 4.5 $\pm$ 3.2% from the low dose and 3.2 $\pm$ 1.9% from the high dose (nonsignificant difference). An estimate of arsenic retained in the skin was not performed, although 27-28% of the arsenic could not be accounted for following decontamination of the skin.

Lowney et al., (2005) conducted follow-up absorption studies with arsenic aged in soil that paralleled the methodology used in the in vivo Rhesus monkey study. The soil samples collected were adjacent to a pesticide production facility that

had historically produced calcium and lead arsenate compounds. The arsenic was resident in the soil for a minimum of 30 years and was primarily in the sparingly soluble iron oxide and iron silicate mineral phases. Small amounts of more soluble calcium arsenate and arsenic trioxide were also detected in the soil. The particle size fraction was sieved to <150 µm and a skin loading of 4 mg/cm^2 on 100 cm^2 of skin was applied. Total dose was 560 µg arsenic and the duration of dermal exposure was 8 hrs on the abdomens of three monkeys. Following fractional correction of arsenic from i.v. dose, urinary excretion of arsenic ranged from 0.01 to 0.24% of the dermally applied dose, but was not statistically greater than background. Negligible absorption was considered to be due to the presence of soil arsenic primarily in sparingly soluble mineral phases. Direct or indirect estimates of arsenic retained in the skin were not performed.

A sweat extraction technique by Nico et al. (2006) was employed to estimate the soluble arsenic that can be made bioavailable for dermal absorption from the aged arsenic soil used in the in vivo monkey study by Lowney et al. (2005). Sweat extraction of this soil resulted in only 1.8% soluble arsenic. However, a second aged soil sample from a different arsenic-contaminated site resulted in 11% arsenic extracted by sweat. Nico et al. (2006) also used the sweat extraction technique to estimate soluble arsenic from soil samples freshly spiked with arsenic. One sample was sieved to <150 µm while another was sieved to 180-300 µm, similar to that used by Wester et al. (1993a) in the in vivo dermal monkey study. Sweat extraction resulted in 45 and 72% soluble arsenic from the <150 and 180-300 µm soil samples, respectively.

B. Supporting Studies

In addition to the monkey in vivo study, Wester et al., (1993a) conducted an in vitro study using human cadaver skin from three separate donor sources with three replicates from each source. The skin was dermatomed to 500 µm, stored refrigerated in Eagle's medium and used within 5 days to preserve skin viability, although elapsed time from death to harvest of skin was not specified. A dose of 0.0004 µg arsenic per cm^2 skin surface exposed was applied. The soil load on the skin samples was 40 mg soil per cm^2 skin area, and phosphate-buffered saline served as receptor fluid. The in vitro exposure period was 24 hours. As performed in the monkey in vivo study, the soil had been sieved to 180-300 µm prior to application, so monolayer coverage was probably not surpassed. Percutaneous absorption through human cadaver skin was 0.76% (0.43% in receptor fluid; 0.33% in skin) after soap and water wash. While the authors did not speculate as to the reduced in vitro dermal absorption compared to monkey in vivo absorption, Kao (1990) noted that both elapsed time from death to harvest of tissues and treatments and storage of the cadaver could have resulted in a large variability in skin permeability.

Dermal absorption of radiolabeled soluble arsenic (as $H_3{}^{73}AsO_4$) freshly applied or aged in two different soils was determined in vitro through dermatomed pig skin cut 200 µm thick (Abdel-Rahman et al., 1996; Abdel-Rahman et al., 1999).

Soil types included a sandy soil with 4.4% organic matter and a clay soil with 1.6% organic matter, with no apparent sieving before application. Arsenic was applied to skin for 16 hrs either alone in ethanol vehicle, immediately after the addition of 30 mg of the soils to skin, or after aging for 3 months in each soil. Soil loading was calculated to be about 47 mg/cm^2. Applying soil to skin and then applying the arsenic does not allow time for arsenic-soil equilibrium. This method of application allows for direct contact of skin with arsenic or vehicle and not from soil, leading to an overestimation of the fractional absorption (Spalt et al., 2009). In addition, monolayer coverage was probably exceeded with a soil loading of 47 mg/cm^2.

With arsenic freshly added to soil, 0.2% of the arsenic penetrated the skin to receptor fluid from both soil types (Abdel-Rahman et al., 1996; Abdel-Rahman et al., 1999). Total dermal absorption including arsenic retained in skin was 10.0 and 6.0% from the sandy and clay soils, respectively. In comparison, pure arsenic found in receptor fluid and retained in skin was 0.4 and 44.2%, respectively. In aged sandy and clay soil, 0.2 and 0.1% arsenic was found in the receptor fluid, respectively. Total dermal absorption in the aged soils was 1.5 and 0.8% from sandy and clay soils, respectively.

Radiolabeled sodium arsenate was applied in vitro to the skin of mice for 24 hrs as a solid compound, in an aqueous solution, or as an aqueous solution in sandy soil (Rahman et al., 1994). Soil was sieved to $\leq$180 µm and contained 58% sand, 34% silt, 8% clay and 1.4% organic matter. Arsenate was freshly applied to soil prior to skin application, with an average soil loading on the skin of 23 mg/cm^2. Absorption increased linearly with the applied dose from all exposure vehicles, with a constant fraction of the dose being absorbed. Total arsenate absorption was as high as 62% of applied dose from 100 µl water vehicle and about 33% of applied dose as the solid. However, absorption of arsenate from soil was less than 0.3% of applied dose, with about one-third penetrating to the receptor fluid.

A dermal exposure study was conducted to assess the potential for arsenic exposure in children in contact with playground equipment and decks treated with the wood preservative chromated copper-arsenate (CCA) (Wester et al., 2004). Methodology was similar to that used by Wester et al. (1993a) in three monkeys to assess dermal arsenic absorption from CCA-treated wood residues. Following 8-hr dermal application, an increase in urinary excretion of arsenic above background was not detectable, indicating virtually no absorption of arsenic from CCA-treated wood residue. The researchers determined that the absorbed dose would need to be in the range of 0.10 to 0.16% of the applied dose to be detectable above background.

The negligible dermal absorption of arsenic from the CCA residues is a result of arsenic chemically bound with other metals (particularly chromium) and ultimately to the wood structure (Nico et al., 2004). The leaching characteristics of soluble arsenic in CCA residues were also investigated by extraction in human sweat

(Nico et al., 2006). The sweat extraction procedure indicated that up to 12% of total arsenic is available for dermal absorption from CCA-treated wood residue. However, only 1.4% soluble arsenic was extracted with sweat from CCA-residue aged in soil near a CCA-treated utility pole. Gastric leaching conditions resulted in up to 2-3 times greater solubilization of arsenic from CCA-treated wood compared to sweat leaching, indicating soil ingestion of CCA-released arsenic can be a health concern.

F.3.1.2 Discussion and Recommendation for Arsenic and Arsenic Compounds ABS

Dermal exposure of skin to arsenic resulting in passage of arsenic through skin to the bloodstream is the primary concern under the “Hot Spots” program. However, arsenic that becomes bound in skin may also have toxicological consequences. Regardless of route of exposure to arsenic, the skin is a critical target organ for arsenic toxicity due to local absorption and binding of sulfhydryl-group-containing proteins (Hostynek et al., 1993). The affinity for sulfhydryl groups leads to arsenic’s accumulation and tenacious retention in keratin-rich tissues such as hair, nails, and skin. Measurement of in vitro percutaneous absorption of As(III) and As(V) by human epidermal skin cultures for 6 hrs shows strong affinity of arsenic for the keratinocytes, with an estimated 30% of As(V) passing through skin being retained compared to over 90% of the As(III) being retained (Bernstam et al., 2002).

Accumulation of arsenic in the skin is characterized by hyperpigmentation, keratoses of the palms of the hands and soles of the feet, and diffuse macular pigmentation or diffuse darkening of the skin on the limbs and trunk, attributed to the reduction and deposition of the element in the metallic state (Hostynek, 2003). Chronic arsenic accumulation in skin increases the susceptibility of the skin to ultraviolet light and is associated with an increased incidence of tumors of exposed skin, although skin cancer is primarily a result of oral arsenical poisoning and characterized by multifocal lesions over the entire body (Hostynek et al., 1993; OEHHA, 1999).

The key in vivo monkey study by Wester et al. (1993a) provides an average fractional absorption of 3.9% based on two dose levels of arsenic that had been freshly added to soil before application to skin. Some limitations are noted for this study. First, the in vivo study did not estimate arsenic retained in skin. However, the researchers followed excretion of arsenic after exposure and noted that excretion of the labeled arsenic was essentially over by day 7. The remaining arsenic bound to skin proteins will probably remain there and not present a risk of reaching the bloodstream.

Secondly, a sieved soil fraction of 180-300 µm was used, which does not reflect the generally smaller soil particle fraction that sticks to skin following dermal contact. Soil sieved to <150 µm is considered more relevant for dermal studies (Spalt et al., 2009). The sieved soil used by Wester et al. may underestimate

fractional absorption. This assumption is supported by the sweat extraction study by Nico et al. (2006), which found a 63% increase in arsenic bioavailability (45% to 72%) from soil sieved to <150 µm as opposed soil sieved to 180-300 µm.

Finally, there is also some question whether the contaminated soil had continuous contact with the skin of the monkeys (Spalt et al., 2009). From the methodology description, the eye patches used to hold the soil in place on the abdomen of the monkeys were a larger volume than the applied soil. Thus, sloughing of soil off the skin probably occurred when the monkeys sat upright.

Together, these limitations indicate that basing an ABS on the monkey study may underestimate the dermal fractional absorption of arsenic. However, the sweat extraction study by Nico et al. (2006) supports the application of an adjustment to account for use of a soil fraction that likely underestimates fractional absorption. A 63% increase in arsenic bioavailability was observed from soil sieved to <150 µm, compared to soil sieved to 180-300 µm, as used by Wester et al. (1993a). A soil sieved to <150 µm better characterizes the soil particle size that adheres to skin. Thus, a 63% increase was applied to the monkey fraction absorption value of 3.9% resulting in an arsenic ABS of 6% when rounded to the nearest whole number.

The in vitro studies reviewed here gave a range of 0.3 to 10% for total absorption following application of freshly spiked soil to skin samples (Rahman et al., 1994; Abdel-Rahman et al., 1996; Abdel-Rahman et al., 1999; Wester et al., 1993a). However, arsenic aged in two soils gave a total dermal absorption of 0.8-1.5% in pig skin in vitro (Abdel-Rahman et al., 1996). As discussed above, it is difficult to reconcile the difference in dermal absorption in pig skin between arsenic freshly spiked in soil and arsenic aged soil due to differences in methodology. Future in vitro studies using human skin and arsenic freshly applied and aged in soils would help assess the impact of arsenic aged in soil.

F.3.2 Beryllium and Beryllium Compounds

Recommended use of default inorganic compound ABS estimate of 3.0%.

F.3.2.1 Studies Considered

No quantitative data could be found regarding the fractional dermal absorption or skin penetration of beryllium (Be) compounds. Be metal powder can oxidize when suspended in synthetic sweat, whereupon the metallic ions may be absorbed in human skin (Larese et al., 2007). However, Be salts are corrosive to skin, and have a high reactivity with protein substrates that result in strong retention in skin (Hostynek et al., 1993). The reaction of beryllium salts with the proteins in skin acts as a strong sensitizer that cause allergic contact dermatitis. Beryllium compounds typically decompose to form the poorly soluble, amorphous oxide (BeO) or hydroxide ($Be(OH)_2$), resulting in tissue granulomas (i.e., compactly grouped cells that replace normally functioning tissue) and ulcers.

Once lodged in tissue, these amorphous beryllium precipitates are excreted at a very slow rate.

Belman (1969) investigated the interaction of beryllium fluoride and beryllium sulfate with guinea pig epidermal tissue in order to explore a mechanism for the delayed allergic skin reaction observed in humans following beryllium exposure. Using both in vitro and in vivo experiments, he reported that beryllium is taken up into the skin and localized primarily to proteins of the epidermis, with little or no apparent binding to stratum corneum or dermis. Exposure caused a localized immune response and rapid destruction of skin cells. Data are not provided, however, regarding the amount of beryllium taken up by the skin cells, or the fate of beryllium following the immunological response (i.e., whether beryllium is then absorbed into the circulation, or sloughed off with cells.)

Petzow and Zorn (1974) reported on the absorption of beryllium through the tail skin of rats exposed to an aqueous beryllium chloride solution spiked with ^{7}Be. The authors stated that within the first hour of exposure there is an increase in the rate of beryllium uptake. After approximately 90 minutes, the dermal flux of beryllium from the aqueous solution is constant. In addition, Petzow and Zorn reported that the amount of beryllium that diffuses through the skin seems to be dependent upon the concentration of beryllium in contact with the skin.

Worker exposure and likely facility emissions of beryllium compounds are mostly in the form of particulates, primarily BeO (Tinkle et al., 2003; Day et al., 2006). For these poorly soluble beryllium particles, dermal exposure is considered to be of toxicological significance. Chronic beryllium disease (CBD) is an occupational disease that begins as a cell-mediated immune response to inhaled beryllium. Although respiratory and engineering controls have significantly decreased occupational inhalation exposures, reduction in occurrence of beryllium sensitization and CBD has not significantly decreased. The lack of worker skin protection has been postulated as a contributor to the persistence of sensitization and CBD in the workplace.

The concentration of antigen required for elicitation of a cell-mediated immune response is significantly smaller than the concentration required for sensitization, therefore, the failure of respiratory exposure limits to lower the rate of disease is likely related to the continued unchecked skin exposure to beryllium particles (Tinkle et al., 2003; Day et al., 2006; Deubner and Kent, 2007). Thus, in workers with significant beryllium skin exposure, the pulmonary exposure required to elicit a subsequent immune response and granuloma formation would be significantly smaller.

To determine if BeO can penetrate the stratum corneum and reach the immunologically active epidermis, Tinkle et al. (2003) conducted a pilot study in which BeO particles were suspended in petrolatum (1 mg/g), painted on the back of shaved mice, and the area covered with surgical tape. The average amount of beryllium applied to each mouse was 70 µg. Excess BeO was removed from the

surface of the flank skin by gentle washing and tape stripping three times immediately following 24-hr exposure. On day 7 or 14 following the exposure, the amount of beryllium in the flank skin of BeO-treated mice was, on average, 1.2 µg/g tissue, thus confirming that BeO is present in the skin.

Additionally, Tinkle et al. (2003) observed in vitro that polystyrene latex spheres <1 µm in diameter, when applied to skin and coupled with flexing motion, can penetrate intact human skin. The researchers proposed that beryllium particles can similarly penetrate the skin.

F.3.2.2 Discussion and Recommendation for the Beryllium and Beryllium Compound ABS

Due to the lack of quantitative data regarding dermal absorption of beryllium, it is not possible to calculate a chemical-specific fractional absorption value for Be salts. The high reactivity of beryllium with skin suggests penetration to the bloodstream in intact skin is small relative to other inorganic metals discussed in this section. However, it is postulated that a primary concern for dermal exposure to beryllium is related to sensitization, which results in much lower inhaled concentrations of beryllium particles required for elicitation of a cell-mediated immune response leading to progression of CBD (Tinkle et al., 2003; Day et al., 2006). This action only requires penetration to the epidermis where the immune response occurs. Considering that full dermal penetration of beryllium to the bloodstream may not be required to enhance or facilitate a toxicological response, and that particles have been shown to penetrate the skin with flexing, it is recommended that an ABS of 3%, based on the mean ABS for the other Hot Spot metals (Cd, Cr(VI), Pb, Hg, Ni) and semi-metals (As), be used for beryllium for screening purposes to assess dermal exposure.

F.3.3 Cadmium and Cadmium Compounds

Recommended point estimate for dermal uptake: 0.2%

F.3.3.1 Studies Considered

A. Key Studies

Wester et al. (1992) examined the percutaneous absorption of cadmium chloride from soil using human cadaver skin in an in vitro system. Donor skin was used within 5 days of harvest and was kept refrigerated in buffered medium until then. The soil used prior to sieving contained 26% sand, 26% clay, 48% silt and 0.9% organic carbon. The soil was sieved to retain particles in the range of 180 to 300 µm. Radiolabeled cadmium (^{109}Cd) was mixed with soil at a concentration of 13 ppb and applied to the skin samples at a soil loading of 20 mg/cm^2 or 40 mg/cm^2. Two donor skin sources were used with replicates for each of the soil concentrations. Human plasma was used as the receptor fluid. At the end of a 16-hour exposure, soil was removed from the samples by soap and water rinse. Percutaneous absorption, calculated as receptor fluid accumulation plus residual

skin concentration after soap and water wash, ranged from 0.08% to 0.2% of applied dose (Table F.1). No significant differences were observed in absorption between skin samples or soil load concentrations.

Table F.1. In Vitro Human Dermal Fractional Absorption of Cadmium Chloride from Soil[a]

Soil Loading	Skin Source	Percentage Applied Dose		
		Receptor Fluid	Skin	Total
40 mg/cm^2	1	0.02 ± 0.01	0.06 ± 0.02	0.08
	2	0.07 ± 0.03	0.13 ± 0.05	0.20
20 mg/cm^2	3	0.02 ± 0.02	0.08 ± 0.06	0.1
	4	0.02 ± 0.02	0.08 ± 0.06	0.1

[a] Data from Wester et al. (1992); n = 3 replicates per skin source

In another experiment, Wester et al. (1992) applied cadmium in water to human skin samples for 30 min, followed by removal of the cadmium solution from the skin surface and continued perfusion of the skin for an additional 48 hrs. No cadmium appeared in the receptor fluid after 30 min of exposure. However, 0.6 ± 0.8% of the dose had diffused into the receptor fluid after 48 hrs demonstrating the capacity of cadmium to be retained in the skin and be slowly systemically absorbed over time.

B. Supporting Studies

Kimura and Otaki (1972) used liver and kidney accumulation of cadmium in rabbits and hairless mice to estimate dermal absorption. A total dose of 30.5 mg Cd (in an aqueous $CdCl_2$ solution) was administered to rabbit skin (n=1) in 5 doses over 3 weeks. Two weeks after the final application, 0.40% of the applied dose was found in liver and kidney combined. In rabbits (n=2), a total dose of 61 mg Cd was administered in multiple cream-like and milk-like ointment applications, resulting in 0.45 and 0.61%of the applied dose, respectively, in liver and kidney combined. The type of ointment vehicle used did not appear to greatly affect the absorption or accumulation characteristics of Cd. Dermal absorption of cadmium in hairless mice, estimated from kidney and liver accumulation, ranged from 0.07-0.27% after a single application of ointment (0.61 mg Cd). Cadmium absorption after multiple ointment applications on hairless mice ranged from 0.59 - 0.87% of applied dose.

Aqueous 1.0, 0.1 and 0.01% cadmium solutions were painted onto the skin of mice and rats and air dried each day for ten days (Lansdown and Sampson, 1996). Perceptible skin damage occurred at the two highest doses, likely

resulting in increased dermal absorption. At the lowest dose, significantly increased skin content of cadmium was observed in both mice (138 ng Cd/g) and rats (248 ng Cd/g). Adequate data to estimate fractional absorption were not provided.

Although no studies estimated dermal absorption of cadmium aged in soils, Aringhieri et al. (1985) reported that 80% of cadmium added to a soil containing high organic matter (14.2%) and high clay content (60%) was adsorbed to soil particles within 10 min of addition to a soil. Tang et al. (2006) observed that bioaccessibility of cadmium (relating closely to absorption following ingestion of soil) in strongly acidic soils spiked with cadmium reached nearly steady state levels as high as 77% after the first week of aging. In soils highly contaminated with heavy metals by industrial sources, the $MgCl_2$-exchangeable fraction of cadmium was about 37% and was considered the most mobile and biologically available heavy metal in the samples examined (Hickey and Kittrick, 1984).

F.3.3.2 Discussion and Recommendation for a Cadmium and Cadmium Compounds ABS

No in vivo studies investigating fractional absorption of cadmium from soil were located. The human in vitro study by Wester et al. (1992) provided the only quantitative data for dermal absorption of cadmium from soil. The retention and concentrating of cadmium in skin with slow systemic absorption demonstrate the necessity for including the cadmium found in exposed skin for estimating an ABS point estimate.

The lack of quantitative in vivo studies and the use of 16 hr rather than 24 hr exposures support a point estimate based on the highest fractional absorption of 0.2%, rather than a the lower estimate of 0.1% (based on an averaging of different skin sources for each of the two soil loadings). In addition, coarse particle soil loadings of 20 and 40 mg/cm^2 may result in a reduced fractional absorption, although the data suggest monolayer coverage of skin was probably not exceeded (Spalt et al., 2009). The high bioavailability and apparent low capacity for aging of cadmium in some soils indicates that sequestration of cadmium in soil will be small relative to other inorganic metals in soil.

F.3.4 Soluble Compounds of Hexavalent Chromium

Recommended point estimate for dermal uptake: 2%

F.3.4.1 Studies Considered

A. Key Study

Czernielewski et al. (1965) exposed guinea pigs to hexavalent chromium (chromium (VI)) as sodium chromate solution labeled with Cr^{51}. A single dose (15 μg sodium chromate in 0.1 ml solution) was applied to a 4 cm^2 shaved area of skin for 24 hours (n=9 animals). Absorption was estimated by measurement of

the Cr^{51} content of the following: urine, feces, blood (1 ml), heart, liver, spleen, adrenals, kidneys, lungs, lymphatics, and skin. Dermal absorption of chromium (VI) was estimated to be 2.9% of the applied dose from the 24 hour exposure. Based on the average blood volume of adult guinea pigs (27 ml), 1.6% of applied dose was found in blood, 1.1% in excreta, and only 0.2% in organs and tissues including skin.

B. Supporting Studies

Chromium in the hexavalent [Cr(VI)] state does not measurably bind with proteins, whereas the trivalent chromic ion [Cr(III)] shows strong affinity for protein in epithelial and dermal tissues (Samitz et al., 1969; Gammelgaard et al., 1992). Thus, Cr(VI) can permeate through skin relatively easily compared to Cr(III). However, skin has the capacity, though limited, to reduce Cr(VI) to Cr(III) resulting in binding of chromium to skin protein and decreasing the rate of diffusion (Gammelgaard et al., 1992; Hostynek, 2003). Binding of chromium in the skin is characterized as irreversible, leading to protein denaturation with formation of permanent depots in the epidermis (Hostynek, 2003). Some of the bound chromium is likely subject to the counter-current effect of continuous sloughing of the outer skin layers, although no studies have attempted to quantify this removal pathway.

To investigate the level of penetration of Cr(VI) into human skin, Liden and Lundberg (1979) cut 10 µm tangential sections of skin biopsies after application of a 0.5% aqueous potassium chromate solution on a 79 mm^2 patch of skin on the back of volunteers. Dermal exposure durations to the chromate were 5, 24, or 72 hrs. Highest chromium levels were found in stratum corneum. Chromium was also found at the dermal-epidermal junction and the upper mid-dermis. Chromium levels differed considerably between different biopsies, but the content of chromium was the same order of magnitude at all exposure durations indicating that a steady state was reached within 5 hrs of exposure.

Mali et al. (1964) measured the disappearance of a radiolabeled chromate solution absorbed dermally in two human volunteers and determined penetration into stratum corneum by tape stripping. Application of a 0.02 ml 0.25% dichromate solution (containing 50 µg Cr(VI)) on a patch to the arm for 12 hrs resulted in the disappearance, and presumed absorption, of 22 µg Cr into the skin. Tape stripping of stratum corneum removed 0.35 µg of radiolabel in the skin.

Systemic uptake of chromium was studied in four human volunteers following a three hour submersion in a tub of water containing 22 mg/L Cr(VI) as potassium dichromate (Corbett et al., 1997). Urinary chromium excretion showed large inter-individual variability. Five-day total Cr urinary excretion above historical background ranged from 17.5 to 1.4 µg, with an average of 6.1 µg. Urine levels of chromium were normal in three volunteers by day 2, although a fourth volunteer excreted elevated levels of chromium up to the end of the experiment

on day 5. Elevated blood and serum levels of chromium were recorded within 1 hr after end of exposure. Chromium content of red blood cells was generally increased about 2-fold, and serum content was increased about 3- to 5-fold. Chromium levels in red blood cells and serum had returned to control levels 2 days after exposure. The systemic uptake rate through skin ranged from 4.1E-04 to 7.5E-05 µg/cm^2-hr with an average of 1.5E-04 µg/cm^2-hr.

Aqueous solutions of Cr(VI) as potassium dichromate, and Cr(III) as chromium trichloride and chromium nitrate were applied in vitro to full thickness human abdominal skin in diffusion cells at a chromium content of 0.034 M (Gammelgaard et al., 1992). Test solutions of 556 µl/cm^2 were applied over a skin surface area of 1.8 or 0.7 cm^2. After 190 hrs exposure of skin to the dichromate, 134 and 12 µg Cr/cm^2 were found in the epidermis and dermis, respectively. Only 0.037 µg Cr/cm^2 was found in the recipient phase. A total Cr(VI) permeation of 15% was calculated. Significantly less Cr(III) from either the trichloride or nitrate was found in skin. Cr(III) content in skin was no more than 9% of the chromium content applied as Cr(VI), with no chromium found in the recipient phase. The lower permeation of Cr(III) was considered a result of the skin acting as a barrier to absorption of the positive Cr(III) ions.

In other experiments by Gammelgaard et al. (1992), application of the dichromate at concentrations of 0.125, 0.25, and 0.5% to skin for 48 hrs showed increased Cr content in skin with increasing concentration, although no Cr was detected in the recipient phase. Total percent Cr permeation of 0.7, 0.7 and 1.1% was calculated for exposure to the 0.5, 0.25 and 0.125% dichromate solutions, respectively. Increasing dichromate concentration (0.5 to 2.5% Cr solution concentrations) with 168 hr exposure did not result in increased Cr content in skin. Long lag times for appearance of Cr in the recipient phase combined with lack of increased skin concentration with time indicates a high binding capacity for Cr that will interfere with diffusion through the skin, although skin binding sites can eventually be exhausted with time. Gammelgaard et al. (1992) also observed the ratio of Cr(VI) to Cr(III) at pH 10 in the recipient phase to increase over 160 hr of exposure. Appearance of chromium as Cr(VI) in the recipient phase increased from about 60% at 40 hrs, to greater than 90% at 120 hrs. This finding indicated reduced capacity for dermal Cr(VI) reduction, eventually resulting in increased Cr(VI) passing through the skin.

Baranowska-Dutkiewicz (1981) found chromium (VI) from aqueous solutions to be readily absorbed by human skin. Seven volunteers were exposed to sodium chromate solutions (0.01, 0.1, and 0.2 M) on an area of the forearm for 15, 30 or 60 minutes, in a series of experiments. The exposure area was covered with a watch glass throughout the exposure period. Absorption was calculated from the difference between the applied and recovered dose of chromium (VI). The authors reported that percutaneous absorption of chromium is dependent on both concentration and time. Specifically, they found that (1) absorption was highest from the 0.01 molar solution (7.7-23% of applied dose) and lowest from the 0.2 molar solution (3.4-10.6% of applied dose), (2) the rate of absorption decreased

as exposure time increased, and (3) the rate of absorption increased proportionally as exposure concentration increased. Individual data were not provided.

Wahlberg and Skog (1963) used disappearance measurements of radiolabeled chromium to estimate dermal absorption of hexavalent chromium in vivo in guinea pigs. Animals were exposed for 5 hours to various concentrations (0.00048 - 4.870 molar) of sodium chromate labeled with ^{51}Cr. Dermal absorption of chromium was confirmed qualitatively by organ analysis. The maximal disappearance of hexavalent chromium was observed from a 0.261 molar solution. Of the 10 animals exposed to this concentration, the mean disappearance percentage per 5-hour period was 4% of the applied dose.

No studies could be located that examined dermal uptake of Cr(VI) from soils. However, chromium fate in soil and soil bioaccessibility studies (gastrointestinal and sweat leaching) have been conducted.

The relationship between Cr(VI) and Cr(III) in soil is a dynamic one, which is affected by soil type and mineral content, pH, solubility, and other factors (Bartlett, 1991; Fendorf, 1995; Stewart et al., 2003). Cr(VI) exhibits greater mobility and less adsorption in soils compared to Cr(III). Organic matter, Fe(II), and sulfides in soils are capable of reducing Cr(VI) to Cr(III), while manganese oxides in soils are capable of oxidizing Cr(III) to Cr(VI). Usually, part of any Cr(VI) added to soil will be reduced instantly, especially under acid conditions. However, high concentrations of polluting Cr(VI) may quickly exhaust the readily available reducing power of the matrix material and excess Cr(VI) may persist for years in soils without reduction.

Oral bioaccessibility of Cr(VI) from aged soils was determined by Stewart et al. (2003) using a physiologically based extraction test designed to simulate the digestive process of the stomach. It would be expected that bioaccessibility for dermal absorption of soil Cr(VI) would be no greater than oral absorption, and oral absorption has been used to estimate dermal exposure to Cr(VI) in soil in previous health assessments (Sheehan et al., 1991).

In general, Cr(VI) bioaccessibility decreased with the aging of Cr(VI) in soils, with decreased bioaccessibility being most rapid for the first 50 days and then slowing dramatically between 50 and 200 days (Stewart et al., 2003). Chromium bioaccessibility was significantly influenced by reduction processes catalyzed by soil organic carbon. Soils with sufficient organic carbon had lower Cr(VI) bioaccessibility values of about 10 to 20% due to enhanced reduction of Cr(VI) to Cr(III). In soils where organic carbon was limited and reduction processes were minimal, considerably higher Cr(VI) bioaccessibility values of 60-70% were recorded.

Soil samples from two chromium waste sites that varied considerably in Cr(VI) concentration were extracted with a synthetic sweat solution to determine the

potential for dermal bioaccessibility of Cr(VI) from contaminated soils (Wainman et al., 1994). The soils examined were contaminated with slag containing chromium from chromate and bichromate production facilities in New Jersey. One set of soil samples contained 710 µg Cr(VI)/g soil and contained chromate blooms, a thin layer of bright yellow crystals on the soil surface. Approximately 83% Cr(VI) was extracted in sweat from the soil with chromate blooms. Adjusting the pH of the soil from pH 5 to 8 had little effect on Cr(VI) extraction. In the other soil, the Cr(VI) concentration averaged 59 µg/g soil. Sweat extraction of Cr(VI) increased from 15 to 32% with increasing soil pH from pH 5 to 8. No Cr(VI) was extracted from the soil adjusted to pH 4. Extraction with distilled-deionized water was also performed, resulting in 76 and 27% extraction from soil with and without blooms, respectively.

Horowitz and Finley (1993) investigated the leaching of Cr(VI) in human sweat from chromite ore processing residue. The New Jersey ore residue originated from the same or similar processing facility as that investigated by Wainman et al. (1994). The human sweat at a pH of 7.2-8.0 extracted < 0.01% of Cr(VI) from the ore samples. Differences in the parent ore and extraction techniques were suspected to have led to the widely varying extraction of Cr(VI) from samples analyzed by Wainman et al. (1994) and Horowitz and Finley (1993).

Oral bioaccessibility studies have also been conducted on the New Jersey slag material (Hamel et al., 1999). Using two different methods, chromium in the slag material had an average bioaccessibility of 34 or 40%, depending on the method used.

F.3.4.2 Discussion and Recommendation for a Hexavalent Chromium (Soluble Compounds) ABS

In the comprehensive in vitro study by Gammelgaard et al. (1992), a measurable increase in Cr(VI) penetrating full thickness human skin could not be detected with 48 hr exposure and only 1.1% of Cr(VI) had been absorbed into the skin. By 190 hrs of exposure fractional absorption of Cr(VI) increased considerably to 15%. The in vitro data indicate Cr(VI) salts have a long lag phase and are slowly absorbed. In contrast, the in vivo human study by Corbett et al. (1997) suggests a very short lag time for appearance of Cr(VI) systemically, with increased Cr levels in the circulatory system within 3 hrs of immersion in a water tank of dilute aqueous dichromate. The human in vivo study by Baranowska-Dutkiewicz (1981) indirectly supports rapid dermal absorption of Cr(VI) with disappearance of aqueous Cr(VI) salt applied to skin for 15-60 min. Consequently, in vitro human exposure likely underestimates the dermal absorption potential of aqueous Cr(VI) solutions that occurs in vivo.

Alternatively, the indirect estimate of up to 23-44% dermal absorption of the applied dose of Cr(VI) salt by Baranowska-Dutkiewicz (1981) and Mali et al. (1964) likely overestimates the dermal absorption potential due to use of a skin occlusion application and reliance on a disappearance method to estimate

absorption. Mali et al. (1964) found only 0.35 µg of chromium in stratum corneum tape stripping even though a total of 22 µg of Cr(VI) was assumed absorbed by disappearance from the skin surface. This finding does not correspond with data by Liden and Lundberg (1979) in which maximal levels of absorbed Cr(VI) was found in stratum corneum.

The 24 hr guinea pig in vivo study by Czernielewski et al. (1965) was the most comprehensive study available in regard to estimating whole body absorption of a dermally applied radiolabeled Cr(VI) solution. Analysis of excreta, blood, and most tissues yielded a fractional absorption of about 2.9%, of which 2.7% was found in excreta and blood. Dermal absorption in experimental animals often overestimates absorption in humans. The in vitro chromate disappearance constants for dermal exposures up to 24 hrs were 3-5 times greater through guinea pig skin compared to human skin (Wahlberg, 1965). However, recognizing that in vitro studies generate slower absorption rates of Cr(VI) than in vivo, the study by Czernielewski et al. (1965) provides a reasonable health protective absorption estimate (2.9%) when considering a human 48 hr in vitro fractional absorption of 1.1% was estimated by Gammelgaard et al. (1992).

To account for the effect of soil vehicle on dermal absorption of Cr(VI), the maximal Cr(VI) bioaccessibility of 83% in synthetic sweat as determined by Wainman et al. (1994) was taken into account. This bioaccessibility estimate was from a soil sample with about 710 µg Cr(VI) per g soil and contained chromate crystals on the soil surface. The contaminated soil probably represents a matrix described by Bartlett (1991) in which high concentrations of Cr(VI) exhausted the readily available reducing power of the soil and excess Cr(VI) persists on the soil surface without being reduced. Thus, multiplying 2.9% by 0.83 and rounded to the nearest whole number provides an ABS point estimate of 2% for Cr(VI) from soil vehicle.

The Hot Spots risk assessment procedures have previously assumed no reduction of deposited Cr(VI) because typically Cr(VI) deposition is modeled without soil sampling monitoring for the Cr(VI)/Cr(III) ratio and without an evaluation of the redox potential of the soil. This assumption may result in overestimation of Cr(VI) soil concentrations in situations where Cr(VI) is readily reduced to Cr(III). Bioaccessibility is determined in part by the Cr(VI)/Cr(III) ratio. The use of soil with high concentrations of Cr(VI) to determine bioaccessibility is not likely to underestimate bioaccessibility under the conditions typically found in Hot Spots risk assessments, where Cr(VI) is deposited over a long period of time and typically results in lower soil concentrations than the 710 µg/g observed in the study by Wainman et al. (1994).

A Limitation for the ABS not discussed above include lack of a factor for absorbed chromium lost through skin desquamation. Studies show that some Cr(VI) will be reduced to Cr(III) in skin and bind to cellular constituents (Gammelgaard et al., 1992; Hostynek, 2003). If this occurs in the stratum corneum, the chromium will likely be removed through desquamation before

systemic absorption can occur. Another limitation includes reliance on studies in which Cr(VI) is applied directly onto the skin (i.e., neat), rather than combined with soil, for estimation of fractional dermal absorption. Kissel (2011) has noted that fractional absorption is dependent on skin loading conditions for application of organic chemicals directly to skin. However, Baranowska-Dutkiewicz (1981) showed that for Cr(VI) the flux through skin increases proportionally with increasing Cr(VI) load applied to skin, resulting in similar fractional absorption values independent of load onto skin. The constraints in estimating fractional absorption for organic chemicals applied neat, which assumes a constant flux through skin, does not appear to be relevant for the metal salt Cr(VI).

F.3.5 Fluoride and Soluble Fluoride Compounds

Recommended use of default inorganic compound ABS estimate of 3.0%.

F.3.5.1 Studies Considered

Excessive exposure to the negatively charged fluoride ion deposited on soil as an aerosol or as a soluble inorganic fluoride salt is known to have toxic effects in animals through ingestion of contaminated soil (Eagers, 1969). However, no quantitative data could be found regarding the fractional dermal absorption of soil-bound fluoride or fluoride compounds following contact with skin. Two animal studies observed elevated fluoride serum levels or systemic toxicity following dermal exposure to concentrated hydrofluoric acid, but immediate skin corrosion was apparent, which would influenced dermal absorption (Derelanko et al., 1985; Boink et al., 1995).

Much of the fluoride naturally present in soils or deposited from facility emissions will generally be in, or strongly adsorbed to, soil particles and is not in a form accessible for uptake by the body (Davison, 1987). Highest levels of water-soluble, or bioaccessible, fluoride in heavily contaminated soils was about 15-20% of total fluoride (Polomski et al., 1982). Among several studies, the bioaccessible fluoride fraction in uncontaminated soils ranged from 0.06 to 7% of total soil fluoride (Gisiger, 1968; Polomski et al., 1982; Milhaud et al., 1989; Buykx et al., 2004).

F.3.5.2 Discussion and Recommendation for a Fluoride and Soluble Fluoride Compound ABS

Due to the lack of quantitative data regarding dermal absorption of soil-bound fluoride, it is not possible to determine an ABS from the data available. Use of a 3% fractional absorption default value, based on the mean of the derived ABS values for Hot Spots metals and semi-metals (As, Cd, Cr(VI), Pb, Hg, Ni), will likely not underestimate dermal absorption of soil-bound fluoride given the highly ionic nature of fluoride and the strong adsorption of deposited fluoride to soil particles.

F.3.6 Lead and Inorganic Lead Compounds

Recommended point estimate for dermal uptake: 3%

F.3.6.1 Studies Considered

A. Key Study

The in vitro dermal absorption of lead oxide (PbO) powder (<10 µm particle diameter) in human abdominal skin was investigated (Filon et al., 2006). Each diffusion cell had a surface area of about 3.14 cm^2 and was filled with 5 mg PbO/cm^2 and with 2 ml synthetic sweat at pH 5.0. At 24 hrs, a median of 2.9 ng/cm^2 (0.06% fractional absorption) had penetrated the skin to the receiving solution and a median of 321.3 ng/cm^2 (6.4% fractional absorption) was absorbed in the skin following surface decontamination. In another experiment, removal of PbO after 30 min exposure did not cause a reduction of Pb penetration in 24 hrs, but did cause a reduction in skin Pb content. This finding suggested that initial rapid absorption of Pb can occur during the first few min of exposure.

B. Supporting Studies

Bress and Bidanset (1991) studied percutaneous absorption of lead in vitro using human abdominal skin obtained from autopsy, and guinea pig dorsal skin. PbO or lead acetate (10 mg) in saline solution was applied to 1.3 cm^2 skin samples. After 24 hours, the lead content of the saline reservoir fluid was measured. The lead content of the skin samples after exposure was not measured. In this experiment, 0.05% of the applied dose of lead acetate was recovered in the reservoir fluid, and less than 0.01% of the PbO. There was no difference between human and guinea pig skin.

Bress and Bidanset (1991) also examined in vivo percutaneous lead absorption in guinea pigs. Lead acetate or PbO, mixed in aqueous solution, was applied to a shaved area (2 cm^2) of the back (300 mg lead per kg body weight). After exposure for 1 week, the animals were killed and lead was measured in blood, brain, liver and kidney. Percent of applied dose absorbed could not be determined from this study. However, the concentration of lead in the measured tissues following lead oxide exposure was similar to that from control animals. In contrast, the lead concentration in measured tissues following lead acetate exposure was greater than controls, although absorption was considered poor, and statistics were not provided.

Moore et al. (1980) studied percutaneous absorption of lead acetate in humans from two commercial hair dye products. The products (one a lotion and one a cream) were spiked with lead-203 (^{203}Pb) and applied to each subject's forehead (n=8) for 12 hours. The preparations were applied in various forms (wet and dried) with periods of one month between each application. Lead absorption was estimated from blood counts, whole-body counts, and urine activity. Results

were normalized for each subject by administration of an intravenous tracer dose of lead chloride.

The mean uptake of ^{203}Pb activity, measured in whole body at 12 hours, was greatest when the preparation was dried and skin was slightly abraded (0.18% of applied dose). The mean absorption including all methods of application (measured in whole body at 12 hours) was 0.058% with a range of 0-0.3%. It has been noted that the presence of colloidal sulphur in the lead acetate formulations used by Moore et al. (1980) may have led to the formation of insoluble lead sulfide, which would be unlikely to be significantly absorbed through skin (Stauber et al., 1994).

In a series of studies in human volunteers, aqueous solutions of inorganic lead salts including lead chloride and lead nitrate were shown to be rapidly absorbed through skin within 3-6 hrs and enter the extracellular compartment, resulting in increased concentrations of lead in the sweat and saliva but not the blood (Lilly et al., 1988; Stauber et al., 1994). However, application of radiolabeled lead (^{204}Pb) to skin of volunteers resulted in measurable increases of ^{204}Pb in the blood but with a very short residence time (Stauber et al., 1994). Preliminary experiments also showed rapid absorption of lead oxide and elemental lead through the human skin of volunteers and detection in the sweat within a few hours. Only $PbCO_3$ was not absorbed through skin. In mice, skin-absorbed lead concentrated more strongly in skin and muscle, and less in blood and other organs compared to intravenously injected lead (Florence et al., 1998).

The authors proposed that the behavior of skin-absorbed lead in the body is different from lead that is ingested or injected, in that lead which passed through skin is in a physicochemical form with low affinity for erythrocytes and a high affinity for extracellular fluid compartments. The implication is that testing blood for lead exposure may not fully account for absorption of lead through the skin.

Stauber et al. (1994) examined dermal lead absorption by placing lead nitrate and lead nitrate spiked with ^{204}Pb on the arms of volunteers for 24 hrs. Rapid increases of lead were observed in sweat samples from the unexposed arm and in saliva, but only small concentrations of lead in blood and urine. However, high levels of ^{204}Pb in blood and urine were measured 2 and 16 days, respectively, after exposure ended suggesting slow absorption of lead into the blood from lead retained in the skin.

In order to quantify dermal lead absorption, 4.4 mg lead (as 0.5 M $Pb(NO_3)_2$) was dispensed onto filter paper and secured with plastic wrap to the left arm of one subject. After 24 hours, the filter paper was removed and the arm was washed. Of the 4.4 mg lead, 3.1 mg was recovered from the filter paper and wash fluid. Using this disappearance technique, the authors estimated that 29% of the lead was absorbed into or through the skin. In two volunteers, the estimated excretion of skin-absorbed ^{204}Pb in the sweat of two volunteers over 24 hrs was 16 and 46 µg lead/L. Assuming an average sweat production of 500 ml/day, the authors

estimated 0.6% and 1.5% of the total lead that was absorbed was excreted in sweat.

Lead acetate or nitrate was also applied to the skin of mice by the researchers in order to quantitate the amount of lead absorbed and retained in organs and tissues (Florence et al., 1998). Forty µl of aqueous solutions of the lead salts (6.4 mg of lead) were applied to a shaved area of skin and covered with Parafilm. Mice were sacrificed and organs and tissues analyzed for lead content after time periods of 2 hrs to 1 week. A total analysis of the organs, feces, and urine showed that, of the 6.4 mg of lead applied to the skin, 26 µg (0.4%) was absorbed through the skin and entered the circulatory system in 21 hrs. This analysis does not appear to include skin-absorbed lead at the site of application. No differences in absorption of the two lead salts were observed. Increased organ content of lead was noted by 6 hrs of exposure, with maximal organ concentrations generally occurring after 24-48 hrs of exposure.

To investigate the stratum corneum depth profiles of lead in lead battery workers, 10 repeated skin strips were collected from exposed skin (dorsal hand) and nonexposed skin (lower back) of 10 volunteers (Sun et al., 2002). Skin areas to be sampled were washed with soap and water, then ethanol, prior to collection in the morning before work. Total lead in stratum corneum strippings ranged from 20.74 to 86.53 µg (mean = 42.8 µg) from the hand, and 8.94 to 28.32 µg (mean = 17.4 µg) from the back. Approximately 20.8 µg (49%) of the total lead in the stratum corneum were in the first two tape strippings. There was a decreasing amount of lead content from both skin regions going from the outer to the inner layers, suggesting both regions had been contaminated with lead. Total amount of lead in the hand, but not the back, was linearly correlated with the amount of lead in blood. These findings indicate the source of lead in skin was from dermal exposure, rather than absorption of lead from the circulatory system into the skin.

Although the lead compound that workers were exposed to was not specified in the Sun et al. (2002) study, the primary lead compounds emitted during lead-acid battery production are identified as PbO and elemental lead (USEPA, 1998; Ruby et al., 1999). Elemental lead particles that are deposited in soils quickly form coatings of highly bioavailable PbO.

The leaching behavior of lead-contaminated soil can be divided into three stages based on the leachate pH: a high alkalinity leaching stage at pH > 12, where Pb formed soluble hydroxide anion complexes and leached out; a neutral to alkaline immobilization stage in the pH range of 6-12, which was characterized by low Pb leachability by adsorption and precipitation; and an acid leaching stage with pH < 6, where leachability increased exponentially with decreasing pH and was characterized as free Pb-ion (Jing et al., 2004). This study indicates that soluble Pb at the neutral pH found in most soils would only be a fraction of the total Pb content of the soil.

Several leaching studies of Pb-contaminated soils suggest the bioaccessible Pb in soil can vary greatly. Within a pH range of 7-8, soluble Pb ranged from less than 0.01% to 48% of total Pb content of soil (LaPerche et al., 1996; Yang et al., 2001; 2002; Jing et al., 2004). In a major Pb contamination due to a paint spill, the Pb soil content was 34,592 mg/kg, which is roughly an order of magnitude greater than many Pb-contaminated soils (Zhang et al., 1998). Soluble Pb at pH 7 was roughly estimated to be 18% of total soil Pb. At pH 5, fractional soluble Pb increased to about 41% of total soil Pb.

F.3.6.2 Discussion and Recommendation for a Lead and Inorganic Lead Compound ABS

The accumulated in vivo absorption data did not provide enough quantitative information to estimate an ABS point estimate of lead including both systemic absorption and that retained in skin. Additionally, no data could be found that measured dermal absorption of lead from contaminated soil. Thus, the lead ABS point estimate incorporated data from an in vitro human study of lead applied neat and soil leaching tests for lead-contaminated soil.

The most comprehensive human data available were the in vitro study by Filon et al. (2006), which observed 0.06% of applied lead penetrating to the receiving solution and 6.4% of applied lead retained in skin following dermal exposure of PbO in a synthetic sweat solution. The skin depth profile of lead shows 49% of the total lead in the stratum corneum was in the first two tape strippings, and might be removed through desquamation prior to systemic absorption (Sun et al., 2002). However, human in vivo dermal exposure data suggest a relatively short lag time for appearance of lead in blood and continual absorption of lead into the blood from the skin reservoir (Lilly et al., 1988; Stauber et al., 1994). Until further studies are conducted to estimate the fraction of lead removed via desquamation prior to systemic absorption, it is presumed that all the lead absorbed in skin is available for systemic absorption.

Although only 0.06% of the lead reached the receiving solution in the in vitro study by Filon et al. (2006), in vitro dermal absorption studies of metal salts generally do not include a full accounting of absorption due to skin shunts such as hair follicles and sweat ducts. Hostynek (2003) noted that these skin shunts swell shut upon hydration during in vitro dermal absorption studies, and can reduce the movement of some dermally applied metal salts directly into lower skin layers. The human in vivo data support the importance of sweat ducts for lead dermal absorption (Lilly et al., 1988; Stauber et al., 1994). In addition, the rapid reduction of lead dermal absorption early during exposure in the Filon et al. (2006) in vitro study has been considered evidence for skin shunts becoming hydrated and reducing lead absorption by these pathways (Hostynek, 2003). These data further support the reasoning that the lead retained in skin observed by Filon et al. (2006) cannot be discounted for potential systemic absorption.

In soil, aqueous leaching studies suggest soluble Pb can vary greatly depending on the soil characteristics. If sweat is the leachate, the pH can range between 4 and 7, with an average in male Caucasians of 4.85 (Wainman et al., 1994). The acidic nature of sweat will likely enhance Pb bioaccessibility from soil compared to the soil pH ranges of 7-8. Because of the wide range of solubilities of Pb in soil, a health protective point estimate based on the solubility of a heavily Pb contaminated soil at pH 5 (average pH of sweat) is warranted. Zhang et al. (1998) observed an approximate 41% Pb solubility at pH 5 from highly contaminated soil (Pb content = 34,592 mg/kg soil). Adjusting the total fractional dermal absorption of 6.46% observed by Filon et al. (2006) by multiplying by the fraction of soluble Pb in a highly impacted soil (0.41) determined by Zhang et al. (1998) results in an ABS point estimate of 3% after rounding to the nearest whole number.

The ABS of 3% for Pb salts is higher than most other metal salts investigated. However, most of the soil leaching experiments used soils that were environmentally contaminated or incorporated time as a factor to control for soil aging. Absorption of Pb salts has also been shown to be high by the oral route relative to other metals, up to 90% absorption in the acidic environment of the stomach (Ruby et al., 1999). A limitation for this ABS is the reliance on studies in which lead is applied neat to skin, rather than combined with soil, for estimation of fractional dermal absorption. Kissel (2011) has noted that fractional absorption is dependent on skin loading conditions for application of organic chemicals directly to skin. However, Baranowska-Dutkiewicz (1981) showed that for Cr(VI) the flux through skin increases proportionally with increasing Cr(VI) load applied to skin, resulting in similar fractional absorption values independent of load onto skin. Thus, dermal absorption of salts of lead applied neat probably is closer to the dermal absorption kinetics of Cr(VI), rather than to organic compounds.

F.3.7 Inorganic Mercury Compounds

Recommended point estimate for dermal uptake from soil: 3%

F.3.7.1 Studies Considered

Quantitative in vivo dermal absorption studies of Hg-contaminated soils have not been performed. A summary of the in vitro dermal studies exposing human and animal skin to Hg-contaminated soil are shown in Table F-2.

A. Key Studies

The dermal bioavailability of $^{203}HgCl_2$ was tested in vitro on dermatomed male pig skin as pure compound or following addition to sandy soil or clay soil (Skowronski et al., 2000). The Yorkshire pig model was chosen due to histological, physiological, biochemical and pharmacological similarities to human skin. The sandy and clay soil consisted of 4.4% and 1.6% organic matter,

respectively, and a majority of the soil particles were in the range of 50-250 µm. A soil loading of 47 mg/cm^2 was calculated from the data provided and the $HgCl_2$ concentration was 5.3 ng/mg soil. Absorption was estimated up to 16 hrs following application.

In general, dermal absorption of Hg was greater from sandy soil than from clay soil. In both soils, the rate of appearance of Hg in the receptor fluid was rapid during the first hour, then decreased to a steady state for the remaining 15 hrs. In sandy soil freshly spiked with Hg, 0.28% and 37.5% of the applied dose had penetrated the skin to the receptor fluid and was bound to skin, respectively, at 16 hrs. In clay soil freshly spiked with Hg, 0.08% and 39.7% of the applied dose had penetrated the skin to the receptor fluid and was bound to skin, respectively, at 16 hrs. For the pure compound, Skowronski et al. (2000) observed a skin penetration of 0.18%, but the amount bound to skin was 66.3%. For Hg aged 3 months in soil, dermal absorption was reduced to 3.3% in sandy soil and 2.6% in clay soil. Only 0.04% and 0.01% of these totals in the sandy and clay soil, respectively, represented percent of applied dose penetrating to the receptor fluid.

B. Supporting Studies

Radiolabeled mercuric chloride ($^{203}HgCl_2$) was mixed with soil and applied in vitro onto fresh human breast skin (obtained within 24 hrs of harvest) for 24 hrs by means of Bronaugh diffusion cells (Moody et al., 2009b). The same amount of $^{203}HgCl_2$ was also applied without soil to human skin samples. The soil had been sieved to 90-710 µm prior to spiking with the Hg salt. The soil mixture (3.2 mg soil) was added to the diffusion cells resulting in a soil loading of 5 mg/cm^2. At 24 hrs, mean percent dermal absorption including the skin depot was 46.6 and 78.3% with and without soil, respectively. The fraction of total absorbed Hg that entered the diffusion cell in 24 hrs was 1.5 and 1.4% with and without soil, respectively.

A radiolabeled mercury compound ($^{203}HgCl_2$) was applied in soil or water vehicle to human skin in vitro (0.5 µg/cm^2 containing 1 µCi) for 24 hours (Wester et al., 1995; Wester and Maibach, 1998c). The investigators used Yolo County soil (26% sand, 26% clay, 48% silt, 0.9% organic) sieved for 180-300 µm particles. Receptor fluid accumulation from either water vehicle or soil vehicle was 0.07% of applied dose. Previously frozen or fresh skin gave similar results. Skin content of mercury from water vehicle averaged 29% of total dose applied. Using soil loads of 5, 10, and 40 mg, skin content of mercury was 10.4, 6.1, and 7.2% of dose applied, respectively.

In other human in vitro studies by the same research group, 5.5% absorption into skin and 0.01% penetration of pure $HgCl_2$ into receptor fluid was observed with a 30 min exposure (Wester et al., 1995; Wester and Maibach, 1998c). Continued perfusion for 48 hrs following the 30 min exposure increased skin absorption and penetration to receptor fluid to 6.3% and 0.09%, respectively, exhibiting the

ability of Hg to migrate through skin after removal of Hg from the skin surface. When the in vitro exposure was increased from 30 min to 24 hrs, mercury skin absorption and penetration to receptor fluid was increased to 35.4% and 0.06%, respectively. No other results or methodology details were provided.

The dermal bioavailability of liquid and soil-bound $^{203}HgCl_2$ was tested on dermatomed human male skin in vitro (Sartorelli et al., 2003). For the liquid vehicle, $HgCl_2$ was added to buffered water solution (pH = 4.0). For the soil vehicle, $HgCl_2$ was added to loam soil consisting of 60% sand, 30% silt and 10% clay sieved to a particle size of <150 µm. Soil loading on skin was about 40 mg/cm^2, which would be greater than monolayer coverage using a particle size of <150 µm. The concentration of $HgCl_2$ was 0.0069 or 0.1190 nmol/cm^3. After 72 hr exposure, any mercury absorbed from soil and penetrating skin to the receiving fluid was below the detection limit. Mean mercury concentrations in the skin were 10.53% of the applied low dose and 15.04% of the applied high dose. Mercury in the liquid vehicle was also applied at two concentrations of 0.0088 and 0.0607 nmol/cm^3. At the low dose, percent of applied dose penetrating skin to the receptor fluid was 1.64 and 4.80% at 24 and 72 hrs, respectively. At the high dose, percent of applied dose penetrating skin to the receptor fluid was 0.34 and 0.93% at 24 and 72 hrs, respectively. Percent of applied dose retained in skin at 72 hrs was 18.93 and 44.97% for the low and high dose, respectively.

TABLE F.2. In Vitro Dermal Absorption Results of Mercuric Chloride from Soil

Study	Species	Exposure time (hr)	Soil fraction (µm)	% Reaching receptor	% Total absorbed fresh	% Total absorbed aged
Skowronski et al., 2000	pig	16	unsieved	0.28 [a] 0.08 [b]	37.8[a] 39.8[b]	3.3[a] 2.5 [b]
Moody et al., 2009	human	24	90-710	1.5	46.6	ND[c]
Wester et al., 1995	human	24	180-300	0.07	7.9	ND
Sartorelli et al., 2003	human	72	<150	0[d]	13	ND

[a] Sandy soil
[b] Clay soil
[c] Not determined
[d] Below the limit of detection

Hursh et al. (1989) studied dermal absorption of mercury vapor in humans. Each of 5 men exposed the skin of one forearm (a single exposure) to vapors with concentrations ranging from 0.88-2.14 ng $^{203}Hg/cm^3$ for periods of 27 to 43 minutes. The rate of dermal uptake of mercury by the arm was quantified by measuring the difference between accumulated radioactivity on exposed and unexposed forearms following exposure. The mean uptake rate for the 5 subjects was reported as 0.024 ng Hg per cm^2 skin per minute per ng Hg per cm^3

air. At this rate, the authors estimate that dermal absorption of mercury from vapor is approximately 2.6% of the rate of uptake by the lung.

In addition, the study protocol by Hursh et al. (1989) included a procedure in which adhesive strips were applied every 3-4 days post exposure for up to 40 days, which regularly removed cells of the stratum corneum from the same marked skin area following exposure. Larger amounts of Hg were stripped at later time points, suggesting that a substantial fraction of the absorbed Hg was probably associated or bound to keratinocytes rather than stratum corneum. Based on the whole body count of radiolabeled Hg and the amount of Hg absorbed in the skin, the authors note that about half of the Hg eventually reached the bloodstream while the remainder was shed by desquamating cells. The data show estimates of 26, 43, 45, 45 and 46% of the dermally absorbed Hg reaching the bloodstream in the five volunteers. It was theorized that the elemental Hg penetrated the stratum corneum as vapor but that in the epidermis, some, but not all, of the Hg became oxidized to mercuric ions. The ions then became fixed or bound in the skin, some of which then moved upward and was eventually shed.

Baranowska-Dutkiewicz (1982) exposed the forearms of eight male volunteers to aqueous mercuric chloride solutions. Aliquots (0.25 ml) of $HgCl_2$ solutions were applied directly to a 22 cm^2 area of skin and covered with a watch-glass. Percutaneous absorption of mercury was calculated as the difference between the amount applied and the amount recovered after the skin and the watch-glass were washed. In order to examine the effect of concentration on uptake, 3 concentrations (0.01, 0.1, and 0.2 M) were applied for 30 minutes. As concentration increased, rate of uptake increased. In order to examine the influence of exposure time on uptake, 0.1 M $HgCl_2$ was applied for 5, 10, 15, 30 and 60 minutes. The authors reported that the average rate of uptake of mercury decreased from 9.3 µg/cm^2/min during a 5 minute exposure, to 2.5 µg/cm^2/min during a 1 hour exposure. The average percutaneous absorption of mercury was calculated for exposures of 5, 10, 15, 30, and 60 minutes resulting in 20%, 29%, 37%, 60% and 64% absorption of the applied dose, respectively.

In vivo application of aqueous $HgCl_2$ (0.1% w/v) to normal human skin followed by biopsy and visualization with electron microscopy found mercury deposits present intracellulary and extracellularly in the stratum corneum within minutes after application (Silberberg, 1972). The presence of mercury in the epidermis was not apparent until 2-4 hrs after application. The finding of immediate absorption of $HgCl_2$ correlates well with the in vivo findings of Baranowska-Dutkiewicz (1982), which observed the disappearance of $HgCl_2$ within 5 min after application to human skin.

An in vivo study in guinea pigs found that dermal absorption of Hg from $HgCl_2$ steadily decreases with increasing dose, suggesting a buildup of a secondary diffusion barrier as a consequence of the electrophilic metal forming irreversible bonds with proteins of the skin (Friberg et al., 1961). Thereby a depot

accumulates in the stratum corneum retarding further penetration in inverse proportion to metal concentration. This secondary barrier build-up retarding absorption was also evident with increasing dermal exposure intervals. $HgCl_2$ applied in vitro on human skin showed greatest percutaneous absorption during the first 5 hrs (Wahlberg, 1965). With later time periods the absorption rate decreased. The average absorption rate over the first 24 hrs was only about one-fourth the rate observed during the first 5 hrs of dermal exposure.

F.3.7.2 Discussion and Recommendation for an Inorganic Mercury Compound ABS

More than 98% of mercury in soils is present as nonalkyl Hg(II) compounds and complexes, with direct deposition a significant component for much of the loading to terrestrial soils (Davis et al., 1997). In the soil, Hg can occur in three different valence states, namely as Hg^0, Hg_2^{2+} and Hg^{2+} (Andersson, 1979). Hg^{2+} forms various complexes with OH^- and Cl^- ions, with the dominating mercuric complexes being $HgCl_2$, $Hg(OH)_2$ and HgOHCl. Only a small fraction of mercuric Hg species occurs free in solution; the major fraction is either bound to or in the soil material. Hg^{2+} and gaseous Hg^0 forms are preferably bound to organic matter in acidic soils, whereas in neutral and slightly alkaline soils, mineral components are active as well. Mercury exhibits a very high affinity for sulfide in reducing environments, forming relatively insoluble HgS (Davis et al., 1997).

Human skin both in vivo and in vitro has been shown to have a large capacity to accumulate metallic mercury vapor or mercury salts (as $HgCl_2$) applied in aqueous solution directly to skin. When freshly mixed with soil, Hg salts appear to have a greater ability for absorption into skin than other metal salts of concern in this section (i.e., Ni, Pb, Cd, etc.). However, similar to other metals, aging of Hg salt in soil significantly reduces the fractional absorption of Hg into skin. Therefore, a fractional absorption of 3% for $HgCl_2$ aged in soil prior to testing was chosen as the basis of the ABS to account for the aging affects in soil.

The Hg ABS is based on the in vitro study in pigs by Skowronski et al. (2000), in which $HgCl_2$ aged in soil for three months resulted in a considerable reduction of fractional absorption compared to $HgCl_2$ freshly mixed with soil. Limitations of this study include use of skin from a non-primate species, less than 24-hr exposure, and likely exceedance of soil monolayer coverage during the exposure. However, the human in vitro studies shown in Table F-2 also have their limitations for estimating fractional absorption, including exceedance of soil monolayer coverage (Sartorelli et al., 2003), or use of soil fractions that do not include soil particles less than 90 to 180 µm, which most commonly adhere to skin (Wester et al., 1995; Moody et al., 2009b).

Given the limitations, it is still unlikely that the ABS will underestimate fractional absorption. While both the human and animal in vitro studies show a large capacity for dermal absorption of Hg salt, very little reaches the diffusion cells (see Table F-2). Other studies reviewed here indicate that some of the Hg^{++} ions

in mercuric salts tend to bind tightly to cellular proteins in all strata of skin, including stratum corneum, which may then impede further diffusion of mercury (Friberg et al., 1961; Silberberg, 1972; Hostynek, 2003). Mercury bound in stratum corneum would likely be removed via desquamation of skin. Hursh et al. (1989) have shown that a considerable portion of absorbed Hg in skin will eventually be lost (up to 50%) due to desquamation.

Nevertheless, the development of a Hg ABS would benefit from human in vitro studies with Hg salts aged in soil, and continued monitoring after 24-hr dermal exposure to better estimate the amount of Hg that reaches the circulation (i.e., reaches the diffusion cells) and how much is likely to be lost due to desquamation. Because the ABS is based on Hg aged in soil, the ABS may underestimate fractional dermal absorption for soils in which a significant fraction of Hg has been very recently deposited on soil, or for soils that are heavily contaminated or saturated with Hg.

F.3.8 Nickel and Nickel Compounds

Recommended point estimate for dermal uptake from soil: 4%

F.3.8.1 Studies Considered

A. Key Studies

Radiolabeled nickel chloride ($^{63}NiCl_2$) was mixed with soil and applied in vitro onto fresh human breast skin (obtained within 24 hrs of harvest) for 24 hrs by means of Bronaugh diffusion cells (Moody et al., 2009b). The same amount of $^{63}NiCl_2$ was also applied without soil to human skin samples. The soil had been sieved to 90-710 µm prior to spiking with nickel salt. The soil mixture (3.2 mg soil) was added to the diffusion cells resulting in a soil loading of 5 mg/cm^2. At 24 hrs, mean percent dermal absorption including the skin depot was 1 and 22.8% with and without soil, respectively. The fraction of total absorbed nickel that entered the diffusion cell in 24 hrs was 0.5 and 1.8% with and without soil, respectively.

In vivo, sequential adhesive tape stripping was implemented to characterize the penetration of nickel salt solutions in methanol and nickel metal powder in human stratum corneum following 24 hr occlusive application to the forearm (Hostynek et al., 2001a; Hostynek et al., 2001b). Hostynek et al. (2001a) investigated stratum corneum depth profiles for chloride, sulfate, nitrate and acetate nickel salts. Penetration of the stratum corneum by nickel salts at levels of 0.001-1% nickel salt was limited and closely related to the counter ion. The total percent dose of each salt recovered in stratum corneum was 26.1, 18.5, 8.8, and 3.3% for the nitrate, acetate, sulfate, and chloride, respectively. Tape stripping of the skin showed that most of the dose remained on the surface or was retained in the superficial layers of the stratum corneum. Depth profiles converged towards non-detectable levels in the lower stratum corneum regardless of concentration

for the acetate, chloride and sulfate. Nickel applied as nitrate is retained at a constant level of approximately 1% of applied dose in the lower layers of the stratum corneum.

The in vitro permeation of 1% aqueous solutions of chloride, sulfate, nitrate, and acetate nickel salts across only the stratum corneum was investigated using human leg skin (Tanojo et al., 2001). An initial surge in permeation rate within the first 24 hrs was observed for the nickel salts, followed by steady-state permeability rate up to 96 hrs that was not significantly different among the four salts. Nickel sulfate penetration of stratum corneum was greatest at 1.09%, whereas nickel nitrate recovery within stratum corneum was greatest at 0.95%. Total absorption (receptor fluid plus bound to stratum corneum) was 1.65, 1.49, 0.92, and 0.12 % for the sulfate, nitrate, chloride, and acetate salts, respectively. Total recovery of absorbed and unabsorbed nickel was virtually complete for all the salts except nickel nitrate, in which 84% recovery was attained.

Permeation of the salts was attributed by Tanojo et al. (2001) solely to the diffusion across the transcellular/intercellular barrier, as hair follicle and gland shunts were shut upon hydration by the aqueous solutions. These pathways swelling shut early during in vitro exposure may explain the decreased rate of absorption of nickel following an initial surge. Lack of ability to account for absorption of nickel via skin shunts may underestimate absorption.

B. Supporting Studies

Nickel reversibly binds to constituents of the epidermis when human epidermis was homogenized and incubated with nickel chloride solutions (Fullerton and Hoelgaard, 1988). Spruit et al. (1965) utilizing human cadaver skin has shown that nickel ions also reversibly bind to the dermis. Nickel powder has also been shown to oxidize when suspended in synthetic sweat, whereupon the metallic ions can be absorbed in vitro through human skin (Larese et al., 2007).

Under the same experimental exposure conditions as used by Hostynek et al., (2001a), nickel metal powder (particle size 3 µm) values were found to decrease from the superficial to the deeper layers of the stratum corneum (Hostynek et al., 2001b). However, nickel was still present at the deepest levels of stratum corneum removed by adhesive stripping, indicating that the metal has likely reached the viable epidermis and has potentially become systemically available. Although the data did not lend itself to estimation of a skin permeation rate, total nickel removed with 20 strips from the skin after 24 hr occlusion with 21.7 mg/cm^2 nickel powder was 38.7 $\mu g/cm^2$ (i.e., approximately 0.18% of the total nickel metal applied was found in the stratum corneum). These data indicated that in intact skin, nickel metal is oxidized to form soluble, stratum corneum-diffusible compounds which penetrate the intact stratum corneum.

Dermal absorption of nickel chloride as $^{63}NiCl_2$ from two different soils was determined in vitro through dermatomed pig skin cut 200 µm thick (Abdel-

Rahman et al., 1997). Soil types included a sandy soil with 4.4% organic matter and a clay soil with 1.6% organic matter. Skin applications included $^{63}NiCl_2$ added immediately after the addition of the two soils (30 mg each) to skin, or after each soil was aged for 6 months with $^{63}NiCl_2$. Nickel chloride was also added alone in ethanol vehicle to separate skin samples. The chemical dose was 113.8 ng/cm^2 and the soil loading was calculated to be 47 mg/cm^2. Monolayer coverage was probably exceeded with a soil loading of 47 mg/cm^2, causing a reduction in the observed fractional absorption.

Following 16 hrs of exposure, 0.3% of freshly applied $^{63}NiCl_2$ in clay soil penetrated the skin to receptor fluid and 12.1% was found bound to skin. No significant difference for dermal absorption from sandy soil was observed. For the nickel solution applied to skin, 0.4 and 57.9% of the dose applied was found in receptor fluid and bound to skin, respectively. In aged sandy and clay soil, 0.03 and 0.05% nickel was found in the receptor fluid, respectively. Only 3.1 and 3.7% of the metal was bound to skin from sandy and clay soil, respectively. Aging nickel in the soils appeared to be complete by 3 months, as further aging in soil for 6 and 12 months did not result in further decreased dermal bioavailability of the metal (Abdel-Rahman et al., 1997; Abdel-Rahman et al., 1999).

Fullerton et al. (1986) examined the permeation of nickel salts, specifically nickel sulfate and nickel chloride, through human full-thickness breast or leg skin in vitro. Skin excised in surgery was exposed to aqueous solutions of 184 μg/cm^2 for each nickel salt for up to 144 hrs. In the first experiment the effect of occlusion on the permeation rate of nickel chloride was examined. Occlusion resulted in a significantly higher permeation rate (approximately 3.6 percent of applied dose) compared with non-occluded exposure (approximately 0.23 percent) after 144 hours.

In the second experiment, nickel ions from a chloride solution were found to pass through the skin about 50 times faster than nickel ions from a sulfate solution. The amount of permeation of nickel chloride was much higher (16%) at 144 hours than nickel sulfate (0.3%). However, dermal penetration of the skin was slow, having a lag-time of about 50 hours. The occluded-skin permeation of nickel chloride was considerably higher in experiment 2 than experiment 1 (9-16% vs 3.6%) and was attributed by the authors to the use of breast skin from different donors.

In another study by the researchers, the stripping method was used in vitro on human full thickness skin following exposure to 5% nickel chloride in a 5% methyl cellulose gel for 96 hrs under occlusion (Fullerton et al., 1988). Nickel penetration from the gel solution gave similar results to nickel penetration of the pure nickel salt. Skin depth profiles found 50.9% was present on and in the stratum corneum (skin was not washed before stripping) with most of the nickel in the upper part of the stratum coeneum, 10.6% in the epidermis, 1.6% in the dermis, and only 0.4% reached the receptor solution.

Although the time frame and doses were different, similar dermal absorption results were obtained by Turkall et al. (2003) with in vitro dermal exposure of pig skin to 64 ng of radiolabeled nickel chloride. Penetration of ^{63}Ni in ethanol through pig skin was 0.4% of initial dose and a total of 58% of the nickel remained in the skin at the end of 16 hrs.

F.3.8.2 Discussion and Recommendation for a Nickel and Nickel Compound ABS

The only study that exposed human skin to soil contaminated with a nickel salt was the in vitro study by Moody et al. (Moody et al., 2009b). However, there is evidence to suggest in vitro tests for dermal absorption of nickel may underestimate absorption in vivo.

Hostynek et al. (2001a) observed a range of 26.1% to 3.3% absorption of applied dose over 24 hrs among four nickel salts tested in vivo on human stratum corneum. However, Tanojo et al. (2001) observed only a range of 1.65% to 0.12% absorption of applied dose over 96 hrs among the same four nickel salts tested in vitro on human stratum corneum. Comparison of these data indicates that reliance on in vitro absorption data probably underestimates the in vivo dermal absorption of nickel salts.

Specifically regarding the nickel chloride salt applied directly to skin, Hostynek et al. (2001a) observed a 24-hr total absorption of 3.3% for human skin in vivo, while Tanojo et al. (2001) observed a 96-hr total absorption of 0.92% for human skin in vitro. These data together suggests a 3.6-fold greater absorption in vivo compared to in vitro absorption.

Although the dermal absorption time used by Tanojo et al. (2001) was 96 hrs, most of the $NiCl_2$ had penetrated the skin in the first 24 hrs (probably greater than 95%) and appearance of nickel into the diffusion cells had attained steady state. Assuming steady state levels of $NiCl_2$ had also been reached in stratum corneum by 24 hrs, it can be estimated that the total absorption of $NiCl_2$ recorded by Tanojo et al. at 96 hrs was similar to that found at 24 hrs.

Applying a 3.6-fold in vivo/in vitro ratio adjustment to the fractional dermal absorption value of 1% for $NiCl_2$ determined by Moody et al. (2009b) results in an ABS value of 3.6% (or 4% when rounded to the nearest whole number). The ABS is similar to the fractional dermal absorption of 2-4% resulting from exposure of pig skin to $NiCl_2$ aged in different soils (Abdel-Rahman et al., 1997; Abdel-Rahman et al., 1999).

F.3.9 Selenium and Selenium Compounds

Recommended use of default inorganic compound ABS estimate of 3.0%.

F.3.9.1 Studies Considered

No quantitative data could be found regarding the fractional dermal absorption of soil-bound selenium (Se) or Se compounds applied to skin.

In dermal absorption studies of Se solutions, Farley et al. (1986) applied a 2.5% selenium sulfide lotion topically overnight on human volunteers. Skin region exposed and surface area covered were not described. Se levels in urine following exposure were significantly increased over control levels, but absorption was considered too slight to result in toxic effects. Repeated overnight treatments in a few volunteers over two days did not result in Se concentrations in the urine which were significantly higher than normal. In another study, increased serum levels of Se could not be measured in human volunteers that applied 2.5% selenium sulfide lotion to their torso overnight (Kalivas, 1993). Used in shampoo as a 1% selenium sulfide concentration, weekly use for a year did not change the normal urinary Se level (Cummins and Kimura, 1971).

Selenium sulfide is insoluble in water and is considerably less toxic via the oral route compared to elemental selenium or ionic forms of water-soluble selenite and selenate salts, such as sodium selenite (Cummins and Kimura, 1971). Lower gastrointestinal absorption of the sulfide salt was thought to be the cause of the lower oral toxicity.

The fraction of applied dose of ^{75}Se internally absorbed following application of selenous acid, a highly water soluble Se compound, onto the pelts of rats was calculated to be 1% per day over a 9-day exposure period (Medinsky et al., 1981).

F.3.9.2 Discussion and Recommendation for a Selenium and Selenium Compounds ABS

Due to the lack of quantitative data regarding dermal absorption of soil-bound Se compounds, it is not possible to determine a chemical-specific point estimate ABS. However, use of a 3% fractional absorption default value for Se and Se salts for screening purposes, based on the mean of the derived ABS values for the Hot Spots metals and semi-metals (As, Cd, Cr(VI), Pb, Hg, Ni), will likely not underestimate dermal absorption of soil-bound Se, given that fractional absorption of highly soluble selenous acid applied neat to the pelts of rats was about 1% of applied dose.

F.4 Point Estimates for Dermal Absorption (ABS) of Organic Compounds

F.4.1 Polychlorinated Biphenyls (PCBs)

Recommended point estimate for dermal uptake from soil: 14%

F.4.1.1 Studies Considered

A. Key Study

The dermal uptake of each of the two commercial PCB formulations Aroclor 1242 and Aroclor 1254 was studied in vivo in female rhesus monkeys (Wester et al., 1993b). Aroclor 1242 is dominated by the tri- and tetra congeners (68 percent) and Aroclor 1254 is dominated by the penta- and hexa congeners (83 percent). Each PCB preparation was adsorbed onto soil particles that before sieving contained 26% sand, 26% clay, 48% silt, and 0.9% organic carbon. The soil was fractionated by particle size to 180 - 300 μm. The soil levels of the PCB preparations were 44 ppm Aroclor 1242 and 23 ppm Aroclor 1254.

The PCB laden soil was applied for 24 hours to a 12 cm^2 area of lightly shaved abdominal skin which was protected by a non-occluded patch. The applied doses were 1.75 μg/cm^2 Aroclor 1242 and 0.91 μg/cm^2 Aroclor 1254. The soil loadings were 40 mg soil/cm^2 skin for both preparations. Following the first 24 hour exposure during which systemic absorption was measured as the content recovered in urine and feces, the patch was removed, the visible soil was removed from the site of application, the treated skin was washed with soap/water, and urine/feces were collected for an additional 34 days. One group of monkeys was exposed to the PCBs intravenously to adjust the cumulative urine/feces recovery of the dermally applied PCBs. The corrected fractional dermal absorption was 13.9% for Aroclor 1242 and 14.1% for Aroclor 1254.

B. Supporting Studies

PCBs are frequently found as complex mixtures of isomers in soil. To determine the effect of chlorine substitution on dermal absorption, Garner and Matthews (1998) applied dermal doses of ^{14}C-labeled mono-, di-, tetra-, and hexachlorobiphenyls to 1 cm^2 areas on the backs of rats for 48 hrs. Dermal penetration varied inversely with the degree of chlorination and ranged from essentially 100% for monochlorobiphenyl to about 30% for the hexachlorobiphenyl. However, the highly chlorinated PCBs tend to have slower metabolism and elimination and remain in the site of exposure longer, resulting in slow diffusion to the systemic circulation.

Mayes et al. (2002) dermally exposed female rhesus monkeys to radiolabeled Aroclor 1260 in soil in a manner similar to that used by Wester et al. (1993b). The soil was classified as sandy silt made up of 20% sand, 54% silt and 20% clay with a total organic carbon content of 5-6%. Sieving to <150 μm prior to application adjusted the total organic carbon content up to 8.7%. Five-hundred

mg of soil either freshly spiked or aged for 88 days with PCBs (about 70 µg PCBs/g soil) was applied to a 12 cm^2 area of the chest/abdominal area and protected by a non-occluded patch. The calculated dermal load was 42 mg/cm^2. One group was exposed to radiolabeled PCBs intravenously to adjust the cumulative urine/feces recovery of dermally applied PCBs. Groups exposed for 12 or 24 hrs to PCBs aged in soil exhibited percutaneous absorption values of 3.43 and 4.26%, respectively, while a group exposed for 24 hrs to soil freshly spiked with PCBs exhibited a dermal absorption value of 4.07%.

Mayes et al. (2002) stated that the reduction in fractional absorption compared to the Wester et al. (1993b) study was due to greater soil content of organic matter, which absorbs highly lipophilic compounds such as PCBs. However, the dermal load of 42 mg/cm^2 used by Mayes et al. likely exceeded monolayer coverage and caused a reduction in fractional absorption. No statistically significant difference was observed between the 12- and 24-hr exposure groups, suggesting PCBs partition quickly into lipid components of the stratum corneum. Likewise, aging of PCBs in soil had no effect on dermal absorption, suggesting rapid binding to the organic fraction of soil. The authors noted that Aroclor 1260 has a slightly higher octanol/water partition coefficient (log K_{ow}) than Aroclors 1242 and 1254 used by Wester et al. (1993b). A higher log K_{ow} would favor greater dermal absorption. However, the higher percentage of congeners with seven or more chlorines in Aroclor 1260 compared to Aroclors 1242 and 1254 tends to reduce dermal absorption, as shown by Garner and Matthews (1998).

The dermal absorption of radiolabeled 3,3',4,4'-tetrachlorobiphenyl (TCB) from liquid and soil mixtures was studied in an ex-vivo Yorkshire-Landrace pig-skin-flap model (Qiao and Riviere, 2000). The soil was described as a dust containing 31.2% sand, 16.8% silt, 53.0% clay (90% kaolinite) and 0.3% organic matter. No particle size fractionation was given. Sixty-five to 70 mg soil containing 200 µg of ^{14}C-TCB (40 $\mu g/cm^2$) was applied onto 5 cm^2 skin surface for 8 hrs, and the area was either left open (non-occlusive) or closed with Parafilm (occlusive). Greatest dermal absorption of TCB occurred from non-occluded soil. Fractional penetration of skin into the perfusate was 0.66%, absorption into dermis and other local tissues excluding stratum corneum was 2.48%, and stratum corneum absorption was 0.90%. Occlusion of the soil mixture significantly decreased dermal absorption 2-3-fold. In addition, dermal absorption from the liquid formulations (acetone, water-acetone mixture, or methylene chloride) was also significantly lower, suggesting TCB dermal absorption data from liquid formulations may considerably underestimate the risk of exposure to TCB in a soil matrix.

Qiao and Riviere (2001) performed a full mass balance in vivo study in Yorkshire-Landrace pigs after iv and dermal exposure to identical doses of 300 µg ^{14}C-TCB. For dermal exposure, TCB in acetone vehicle was applied to a 7.5 cm^2 abdominal area of three pigs and protected by a glass chamber with holes, followed by covering with a nylon sieve screening. Urine and feces were collected for 11 days, with quantitative tissue analysis and tape stripping of the

TCB-exposed dermal region conducted at the end of the 11 day exposure. On average, about 70-71% of the applied dermal and iv doses were recovered. After iv dosing, a total of 60% of the dose was excreted via urinary and fecal routes with 8% of the initial dose remaining in body tissues. However, when TCB was given topically, the total excretion was only 5% but with a much larger tissue residue of 16%. The fraction of applied dermal dose reaching the systemic circulation was estimated at 22%, with 0.85% of the applied dose in stratum corneum following tape stripping of the TCB-exposed skin.

Because of the higher tissue residue levels following dermal absorption of TCB, the researchers noted that dermal absorption of chemicals similar to TCB may be underestimated without a full mass balance analysis (Qiao and Riviere, 2001). In other words, estimating dermal absorption by comparing urinary excretion or blood AUC data with data obtained by the iv route (which represents 100% absorption) would underestimate actual TCB dermal absorption. Use of these indirect methods of absorption would provide a calculated dermal absorption of 6.3-10%.

In addition to their in vivo monkey study described above, Wester et al. (1993b) also estimated in vitro dermal absorption of PCBs through human skin from soil. The percent dose penetrating to the receptor fluid after 24 hr exposure was 0.04% for both Aroclor 1242 and Aroclor 1254. The percent dose absorbed in skin was 2.6% for Aroclor 1242 and 1.6% for Aroclor 1254. The low in vitro dermal absorption compared to their in vivo monkey study results was thought to result from tissue viability issues or solubility limits with receptor fluid. However, in vitro dermal absorption and penetration using water as the vehicle resulted in a fractional absorption of 44-46% for both PCB formulations.

The dermal absorption of purified TCB from soil was studied in rat and human skin in vitro (USEPA, 1992). The soil was comprised mostly of silt with an organic carbon content of 0.45% and a particle size range within 0.05-2 mm. The TCB concentration in the soil was 1000 ppm and soil loading was 10 mg/cm^2 for the rat skin and 6 mg/cm^2 for the human skin. After 96 hours, 7.10% of the applied dose had penetrated the human skin into the perfusate, with another 0.26% remaining in skin after washing. In comparison, total dermal absorption in rat skin was over 4-fold higher. A similar experiment was conducted with rat skin in vitro using a soil with a high organic carbon content of 11.2%. Total dermal absorption of TCB was reduced over 3-fold compared to total absorption from the low organic carbon soil.

Dermal absorption of PCBs was estimated by the disappearance method in a single volunteer exposed to a mixture of ^{13}C-labeled tetra-, penta-, hexa-, and heptachlorobiphenyls (Schmid et al., 1992). Five mg of the PCB mixture were applied to a 4 cm^2 cotton cloth in methylene chloride vehicle and dried. The cotton cloth was then applied to the tip of the forefinger or inner side of the forearm without occlusion for 8 hrs. After recovery of PCBs from the carrier and skin surface, disappearance of the remaining label suggested dermal absorption

was 7 and 47% of total dose applied to finger and forearm, respectively. However, plasma concentrations of ^{13}C-label were at or below the limit of detection (10-20 pg/ml) and were not considered reliable. Application of PCBs to aluminum foil, then rubbed into the skin of the forearm for 10 min, resulted in a fractional absorption of 8% by the disappearance method and a plasma concentration of 56.3 pg/ml. The authors suggested that the lack of measurable serum levels of PCBs was partly due to evaporative loss during exposure.

Dermal absorption of HCB in vivo and in vitro was investigated in young (33 days of age) and adult (82 days of age) female rats (Fisher et al., 1989). Young rats absorbed 3.37 times as much HCB dermally as adults in the first 6 hrs of exposure. This resulted from a lag time for penetration of about 1 hr in young and 4 hrs in adult rats. At 72 hrs in vivo dermal penetration was 35% in young and 26% in adults compared to 1.5% for young and 1.0% for adult as measured with a continuous flow in vitro system, and 2.9% for young and 1.9% for adults as measured with a static in vitro system. By 120 hrs both young and adult rats have the same cumulative dermal absorption.

F.4.1.2 Discussion and Recommendation for a Polychlorinated Biphenyl ABS

The Wester et al. (1993b) study provided the highest fractional dermal absorption value (14%) for PCBs in soil among the in vivo experimental animal species considered most relevant for human exposures (i.e., monkey and pigs). Similar to the Wester study, Mayes et al. (2002) used Rhesus monkeys to estimate dermal absorption of PCBs, but obtained fractional absorption values of only 3-4%. Suggested reasons for the lower value include a greater proportion of highly chlorinated congeners, which reduce absorption. However, this may not be an issue because Wester observed similar fractional absorption values using an Arochlor (1242) dominated by tri- and tetra-congeners, and an Arochlor (1254) dominated by penta- and hexa-congeners. Use of a soil with higher organic carbon content may have also resulted in a lower fraction absorption. Additionally, Spalt et al. (2009) notes that Mayes et al. probably exceeded monolayer coverage during the experiment, whereas Wester et al. did not.

The Wester et al. and Mayes et al. studies also used an indirect mass balance adjustment for dermal absorption by comparing excretion of dermally-applied PCBs to excretion of iv administered PCBs. Qiao and Riviere (2001) showed that this may underestimate dermal absorption up to 2- to 3-fold due to greater organ and tissue content of PCBs following dermal absorption compared to PCBs that were injected by the iv route. Thus, the highest absorption fraction estimate (14%) by Wester et al. (1993b) is recommended as the best health protective value.

Wester et al. (1993b) did not age the PCBs in soil prior to dermal application on the monkeys. However, Mayes et al. (2002) observed that aging of PCBs in soil did not reduce dermal absorption compared to freshly spiked soil.

In vitro dermal absorption studies were not considered for estimating the ABS. Comparison studies applying PCBs both in vivo and in vitro suggest that estimating dermal fractional absorption with an in vitro system would underestimate dermal absorption obtained by in vivo methods (USEPA, 1992; Wester et al., 1993b). A reason for this underestimation may be the limited lipophilicity of the receptor fluid used with the in vitro systems.

F.4.2 Polychlorinated Dibenzo-p-dioxins and Dibenzofurans

"Dioxin" emissions are reported as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) equivalents. Therefore, for purposes of the Hot Spots program, all polychlorinated dibenzo-p-dioxins and dibenzofurans are considered to have the same dermal absorption characteristics as TCDD.

Recommended point estimate for dermal uptake from soil: 3%

F.4.2.1 Studies Considered

A. Key Studies

The dermal absorption of TCDD from high organic (HOS) and low organic (LOS) soils in rats in vitro, and in human skin in vitro and rats in vivo from LOS only, was investigated during exposure intervals up to 96 hours (U.S. EPA, 1992; Roy et al., 2008). The LOS was comprised mostly of silt with an organic carbon content of 0.45% and a particle size range within 0.05-2 mm. For the in vitro studies, the TCDD concentration in the LOS was 1 ppm with soil loading of 10 mg/cm^2 on the rat skin and 6 mg/cm^2 on the human skin. After 24 hrs, 0.28% and 1.17% of the applied dose had penetrated human and rat skin, respectively, to the receptor fluid (Table F-3). Although the dose of TCDD remaining in skin was not determined at 24 hrs, the 96 hr exposure estimate in human and rat skin following skin surface wiping was 0.17 and 1.41%, respectively. The percent of applied dose reaching the receptor fluid at 96 hrs was 2.25% in human skin and 6.32% in rat skin.

The percent of dose absorbed from LOS by rats in vivo was 7.9% at 24 hrs and 16.3% at 96 hrs (Table F-3). TCDD absorbed was estimated indirectly by dividing the percent of applied dose found in the excreta by the fraction of applied dose in the excreta at the same time after i.v. administration. However, TCDD systemically absorbed at 96 hrs was also quantified in all urine, feces and tissues, resulting in 16.3% of dose absorbed. To derive an ABS for human *in vivo* uptake of TCDD from LOS (0.45% organic carbon content) and HOS (11.2% organic carbon content), USEPA (1992) applied corrections by direct ratios to account for rat in vivo, rat in vitro, and human in vitro data. For human TCDD absorption from LOS, the in vivo absorption in rat at 24 hrs was multiplied by the ratio of human to rat total absorption in vitro measured at 96 hrs. The 96 hrs data were used because this was the only measurement in which TCDD in skin was quantified. The final ABS was 2.5% (8.0% x 2.42% / 7.74%).

Table F.3. Percent Dermal Absorption of TCDD over Time from Low Organic Soil[a]

Time (hr)	Rat – in vivo	Rat – in vitro	Human in vitro
24	7.9	1.17	0.28
96	16.3	6.32	2.25
96 (Dose in skin sample after wiping)	NA[b]	1.4	0.2
96 (Total)	16.3	7.7	2.4

[a] Data from US EPA (1992) and Roy et al., 2008
[b] Not applicable

Roy et al. (2008) note that steady state conditions for the TCDD concentration in skin from LOS are reached by 24 hours for the in vitro experiments. Thus it should be reasonable to assume that the amount in the skin after 96 hours is about the same as after 24 hours. The researchers also observed that the rat in vivo percent absorbed results were about twice as high as the rat in vitro results after 96 hours. Assuming the human in vitro results would operate in a similar fashion; Roy et al. obtained a human 24-hr fractional TCDD absorption rate of 0.96% (0.48% x 16.3% / 7.7%). Additionally, a fractional absorption value of 0.1% was derived for TCDD absorbed from HOS (soil with an organic content >10%).

Alternately, it may be more relevant to multiply the rat in vivo percent absorbed at 24 hours (7.9%) by the estimated in vitro rat-to-human ratio for total percent TCDD absorbed at 24 hours (0.48% / 2.75%), rather than rely on any of the results from 96 hr exposure. The resulting human 24-hr fractional TCDD absorption rate by this method is 1.4%.

B. Supporting Studies

Shu et al. (1988) applied soil-bound TCDD to the backs of rats, clipped of hair. Laboratory contaminated TCDD soil was prepared from soil obtained from Times Beach MO and determined not to contain TCDD before the experimental addition of the chemical. Environmentally contaminated soil was also obtained from Times Beach, MO and determined to contain 123 ppb TCDD after sieving through a 40-mesh screen. The organic carbon content of the soils was not specified. Soil loading was 20.8 mg soil/cm^2 skin on a total skin area of 12 cm^2. The TCDD content of the laboratory prepared soil was 10 or 100 pg/mg soil. Occlusion of the skin was minimized by the use of a perforated aluminum eye patch to cover the exposed area. Dermal exposure duration to the TCDD-laden soil was 24 hours and recovery was measured 48 hours following initiation of exposure. In some experiments, 0.5 or 2.0 percent (w/w) used crankcase oil was added to the soil before the addition of TCDD.

Following 24 hour dermal exposure + 24 hour post-exposure (total of 48 hours from initiation of exposure), the TCDD content of the liver was determined. The

uptake of TCDD under the experimental protocols ranged from 0.54 ± 0.06 to 1.01 ± 0.22% and averaged 0.76 ± 0.16%. The percent uptake of TCDD in liver was not affected by the applied TCDD dose (12.5 or 125 ng/kg BW), the presence of crankcase oil in the soil, the use of soil that had been environmentally contaminated with TCDD, or by the use of haired or hairless rats.

Peak liver concentrations for TCDD administered orally and dermally were used to correct for incomplete absorption in the calculation of relative dermal absorption. The calculation is based on the assumption that the source of fecal TCDD following oral exposure is unabsorbed TCDD. The estimated relative dermal bioavailability is 1.5% from laboratory-contaminated soil and 1.6% from environmentally contaminated soil.

Diliberto et al. (1996) note that during the first 48 hours following oral exposure, TCDD in rat feces included both unabsorbed TCDD and absorbed TCDD that was excreted in bile. However the data suggest that at 48 hours, absorbed TCDD contributes only about 10% of the fecal TCDD.

Poiger and Schlatter (1980) applied radiolabeled TCDD in a soil/water paste formulation (26, 350, or 1300 ng in 14.3 mg soil/cm^2 skin) to the backs of hairless rats and measured the appearance of label in the livers. The soil (organic carbon content unspecified) was taken from the Seveso region and was TCDD-free. Measurements were taken 48 hours after the initiation of a 24 hour exposure period.

The average percentage of dose in the liver after dermal application was 0.05, 1.7, and 2.2% for the 26, 350, and 1300 ng dose groups, respectively. The authors noted that other researchers observed that 70% of total body burden of administered TCDD is found in the liver of rats. Using this estimate, the corrected dermal absorption of total applied dose is 0.07, 2.4, and 3.1% for the 26, 350, and 1300 ng dose groups, respectively. The authors also compared the liver uptake of dermally applied TCDD from a soil/water paste to the uptake from methanol, and found the soil/water paste caused a reduction in the fractional uptake (compared to methanol) of 12 percent (1.6 ng TCDD/kg BW) or 15 percent (5.8 ng/kg BW).

TCDD in acetone vehicle was applied to human skin in vitro to estimate the capacity of skin to store TCDD (Weber et al., 1991). Although TCDD did not readily penetrate the skin into the saline receptor fluid (0.03% of dose) after 16.7 hrs exposure, a major portion of the dose was found in skin. The percent of dose absorbed in skin at 16.7 hrs was 56% at a skin loading of 65 ng/cm^2, and 40% at a skin loading of 6.5 ng/cm^2.

Age may be a factor in the absorption of TCDD-like compounds. Anderson et al. (1993) applied radiolabeled TCDD in acetone (111 pmol/cm^2 applied over 1.8 cm^2) to the interscapular region of 3-, 5-, 8-, 10-, and 36-week-old rats and measured dermal absorption 72 hrs later. Dermal absorption was greatest in

3-week-old rats at 64%, decreasing to about 40% in 5-, 8-, and 10-week-old rats, and to about 22% in 36-week-old rats. Although the reason for the age-related changes in dermal absorption was not explored, the authors suggested increased lipids in skin of the young may be a factor.

F.4.2.2 Discussion and Recommendation for a Polychlorinated Dibenzo-p-dioxin and Dibenzofuran ABS

Human skin has the capacity to store TCDD in vitro (Weber et al., 1991; Roy et al., 2008). Once absorbed in skin, lipophilic compounds such as TCDD are anticipated to be eventually absorbed into the systemic circulation. Data for another lipophilic pollutant, lindane, indicates that the chemical retained in skin will be eventually systemically absorbed (Dick et al., 1997a).

Several methods for assessing the dermal exposure data by US EPA (1992) and Roy et al. (2008) were employed above to obtain a total fractional absorption (i.e., amount that reached the bloodstream + amount retained in skin) for TCDD ABS. Since the fractional dermal absorption values presented in this document are based on 24-hr exposure, the most relevant means for estimating an ABS is to rely only on the 24-hr absorption results. The resulting human 24-hr fractional TCDD absorption rate by this method is 1.4%. Roy et al. (2008) employ a monolayer adjustment factor in their assessment, noting that the human in vitro skin test used a soil load of 6 mg/cm^2, which was greater than monolayer load by a factor of 2. Multiplying by this factor, the 24-hr TCDD fractional absorption for human skin is estimated at 2.8% for LOS, which is then rounded up to 3%.

Although both Shu et al. (1988) and Poiger and Schlatter (1980) estimated dermal absorption fractions in rats near 2%, neither study specified the organic carbon content of the TCDD-contaminated soil. The organic carbon content of soil is a major determinant for TCDD dermal absorption. At 96 hrs, USEPA (1992) noted that the ratio of TCDD absorption from low organic carbon soil (0.45% organic carbon) in rat skin measured in vitro to absorption from high organic carbon soil (11.2% organic carbon) in the same system was 7.5. Without the organic carbon content of the soil, it is difficult to compare the findings of Shu et al. (1988) and Poiger and Schlatter (1980) with that of the USEPA study.

TCDD aged in soil prior to dermal application had little effect on absorption, which is supported by the long half-life of TCDD in soil. Shu et al. (1988) observed similar dermal absorption estimates when TCDD was freshly added to soil in the lab and soil that had been environmentally contaminated with TCDD and presumably aged in the soil. In addition, soil aging of polychlorinated biphenyls (PCBs), a group of soil contaminants with some structural similarities to TCDD, is not a significant factor for dermal absorption (Mayes et al., 2002). On the other hand, oral studies of soil-laden TCDD do indicate aging to be factor in the reduction of TCDD intestinal absorption (Poiger and Schlatter, 1980).

F.4.3 Polycyclic Aromatic Hydrocarbons as Benzo[a]pyrene (BaP)

Recommended point estimate for dermal uptake from soil: 13%

Field studies of workers have shown that dermal absorption of PAHs may be significant. Dermal absorption of PAHs, based on the urinary excretion of 1-hydroxypyrene (1-HP), has been documented among petrochemical industry workers, including those digging in PAH-contaminated soil (Boogaard and van Sittert, 1995). Although no attempt was made to quantify the extent of absorption through dermal and inhalation routes, the results of the study strongly suggest dermal uptake is substantial and is mitigated by the use of appropriate protective clothing. Elovaara et al. (1995) compared the levels of urinary 1-HP among 6 creosote workers compared to that expected from the inhalation of the known air levels of PAHs containing $\geq$ 4 rings. Higher levels of urinary 1-HP were observed than could be accounted for solely from the inhalation route of exposure.

F.4.3.1 Studies Considered

A. Key Study

In Wester et al. (1990b), the dermal uptake of soil-bound BaP was studied in vivo in four rhesus monkeys. The systemic absorption of soil-bound BaP was based on urinary excretion following exposure of 12 cm^2 abdominal skin to 10 ppm BaP in soil at a soil loading of 40 mg/cm^2 skin. A nonocclusive cover protected the dermal application site. Prior to sieving to approximately 180-320 µm diameter, the soil composition was 26 percent sand, 26 percent clay, and 48 percent silt with 0.9 percent organic carbon content.

Exposure duration to the chemical laden soil was 24 hours, during which time urine was collected. The cover was removed, visible soil was collected, and the skin application site was washed with soap and water. Urine was then collected for 6 additional days for a cumulative recovery period of 7 days. Incomplete excretion of BaP was corrected by the urinary excretion of BaP following intravenous (iv) administration of the PAH in acetone. The authors report a mean 24 hour dermal absorption factor of 13.2 $\pm$ 3.4 percent (Table F.4).

Radiolabeled BaP (^{14}C-BaP) was mixed with commercial gardening soil and applied in vitro onto fresh human female breast skin (obtained within 1 day of harvest) for 24 hrs by means of Bronaugh diffusion cells (Moody et al., 2007). The same amount of ^{14}C-BaP was also applied without soil to human skin samples. The soil had been sieved to <710 µm prior to spiking with BaP. The soil mixture (3.2 mg soil) was added to the diffusion cells resulting in a soil loading of 5 mg/cm^2. At 24 hrs, the mean total percent dermal absorption including the skin depot was 14.8 and 56.4% with and without soil, respectively. The fraction of total absorbed BaP that entered the diffusion cell in 24 hrs was 7.2 and 11% with and without soil, respectively.

B. Supporting Studies

Yang et al. (1989) studied the in vivo systemic absorption in rats of BaP in soil, fortified with petroleum crude oil (1 percent (w/w)) to which ^{3}H-BaP was added. The soil, which consisted of 46 percent sand, 18 percent clay and 36 percent silt, with an organic content of 1.6 percent, was sieved to a particle size <150 µm. The final BaP level in the soil was 1 ppm and the soil loading was 9 mg/cm^2.

After 24 hours, 1.1 percent of the radioactive label was found in the rat urine and feces; no label was found in the tissues. By 96 hours (4 days) the cumulative total of radioactive label in the excreta + tissues was 9.2 percent, of which 5.8 percent was in the feces. The dermal uptake rate was estimated to be 0.2 ng/cm^2/day. Remaining BaP retained in skin at the site of application was not determined. In vitro absorption of BaP in soil was also determined in rats using a similar exposure protocol. Very good correlation was observed between the in vivo and in vitro data.

In conjunction with the in vivo dermal absorption studies in monkeys, Wester et al. (1990b) also conducted BaP dermal absorption experiments with viable human skin in vitro. Under the same soil and loading conditions of the in vivo monkey study, BaP-laden soil was applied to skin samples (dermatomed to 500 µm thickness) for 24 hrs. The percentage of applied dose in skin and in human plasma receptor fluid was 1.4 and 0.01%, respectively. When acetone was used as the vehicle under the same exposure conditions, BaP found in receptor fluid and in skin was 0.09 and 23.7% of applied dose, respectively.

Dermal absorption of ^{3}H-BaP from two different soils was determined in vitro through dermatomed pig skin cut 200 µm thick (Abdel-Rahman et al., 2002). Soil types included a sandy soil with 4.4% organic matter and a clay soil with 1.6% organic matter. Skin applications included: BaP applied as the pure compound; BaP applied immediately after the addition to each soil type (30 mg each); and pre-sterilized soils aged for three months with BaP. The chemical dose was 1.67 mg/kg and the soil loading was calculated to be 47 mg/cm^2.

Following 16 hrs of exposure, 0.2% of freshly applied BaP in sandy soil penetrated the skin to receptor fluid and 8.3% was found bound to skin. In clay soil, 0.1% of freshly applied BaP was found in the receptor fluid and 3.3% was bound to skin. In comparison, pure BaP applied to skin resulted in 0.2 and 75.8% of the dose found in receptor fluid and bound to skin, respectively. For BaP aged in either sandy or clay soil, 0.1% was found in the receptor fluid. Only 3.7 and 1.7% were bound to skin from sandy and clay soil, respectively. Aging BaP in the soils for three months decreased total dermal adsorption by about 2-fold compared to BaP freshly applied to the soils.

Table F.4. In Vivo and In Vitro Dermal Absorption Results of Pure BaP Freshly Applied or Aged in Soils

Study	Species Treatment	Exposure time (hr)	Soil fraction (µm)	% Total absorbed fresh	% Total absorbed aged
Wester et al. 1990b	monkey in vivo	24	180-320	13.2	ND [a]
Yang et al., 1989	rat in vivo	96	<150	9.2	ND
Moody et al., 2007	human in vitro	24	<710	14.8	ND[c]
Wester et al., 1990b	human in vitro	24	180-320	1.4	ND
Abdel-Rahman et al., 2002	pig in vitro	16	unsieved	8.5[b] 3.4[c]	3.8 [b] 1.8 [c]

[a] Not determined
[b] Sandy soil
[c] Clay soil

Studies were conducted to measure in vitro absorption of BaP through human skin (previously stored frozen) from contaminated soils at manufactured gas plant (MPG) sites. These sites were impacted by PAHs in lampblack, a residue produced from the pyrolysis of oil to produce gas. Roy et al. (1998) collected nine soils from three MPG sites containing targeted PAHs at levels ranging from 10 to 2400 mg/kg. Dermal penetration rates of target PAH from the soils were determined using ^{3}H-BaP as a surrogate. Soils were sieved to <150 µm prior to analytical characterization and loaded onto skin sections at 25 mg/cm^2. Dermal absorption tests ran up to 144 hrs. The recovery of radiolabel in the receptor fluid ranged from 0.19 to 1.0%, while radiolabel absorbed in skin ranged from 0.4 to 1.0%. The highest percent of applied dose (receptor fluid + skin) from a contaminated soil was 1.9%.

Contaminated soils were collected from 7 oil-gas MPG sites in California to assess dermal absorption of BaP in vitro (Stroo et al., 2005a; Stroo et al., 2005b). The soil was sieved to <150 µm and loaded onto human skin at 10 mg/cm^2. The skin samples were dermatomed to a thickness of 350 µm. The percentage of applied dose absorbed across skin over 24 hrs ranged from 0.14 to 1.05%. The lower absorption of BaP in the lampblack samples compared to the Wester et al. (1990b) study was attributed to soil aging effects, but also to tighter binding of BaP to lampblack. Lampblack tends to bind hydrocarbons more tightly then conventional soil organic matter.

To investigate effects of soil loading and aging on PAH dermal absorption, Roy and Singh (2001) loaded PAH-spiked soil onto human skin sections at 1, 2.5, 5 and 10 mg/cm^2 following aging of the PAHs in soil up to 110 days. A field soil was sieved to <150 µm, resulting in a total organic content of 0.43%. The soil

was spiked with coal tar and ^{3}H-BaP to achieve a final soil BaP concentration of 65 ppm. At soil loadings of 1 and 2.5 mg/cm^2, approximately 1% of the applied dose was in the receptor fluid at 24 hrs. The percent of applied dose absorbed decreased with increasing soil loadings of 5 and 10 mg/cm^2, respectively, indicating skin loading above monolayer coverage. In the aging experiment, the dermal bioavailability of coal-tar-derived BaP was reduced by about half by day 110 compared to the soil freshly spiked with ^{3}H-BaP.

The in vitro dermal absorption of BaP applied in acetone to full-thickness skin was compared among six mammalian species (Kao et al., 1985). The percent of applied dose permeating fresh, viable skin in 24 hrs was approximately 10% in mice, 3% in marmosets and humans, 2% in rats and rabbits, and <1% in guinea pigs. However, permeation through skin rendered non-viable by previous freezing was <1% of applied dose in all species. Permeation was accompanied by extensive first-pass metabolism of BaP in viable skin of all species. Nearly half the BaP that permeated viable human skin was attributed to BaP metabolites. In non-viable skin, essentially only unchanged BaP was detected in the receptor fluid.

PAHs have been shown to be poorly absorbed through skin from solids. No percutaneous penetration of PAHs from coal dust occurred across human skin in vitro (Sartorelli et al., 2001).

F.4.3.2 Discussion and Recommendation for a Polycyclic Aromatic Hydrocarbon ABS

A fractional dermal absorption of 13% determined in a primate species in vivo represents a health-protective estimate of human systemic absorption of pure BaP freshly applied to an agricultural soil (Wester et al., 1990b). In support, a similar in vitro fractional absorption (14.8%) was attained by Moody et al. (2007) for 24-hr exposure of human skin to BaP-contaminated soil. The work by Wester et al. and Moody et al. were also one of the few BaP exposure studies that did not exceed monolayer soil coverage of the skin, although the coarse particle soil loadings used in the monkey study may have resulted in a lower fractional absorption.

The only other in vivo study of BaP dermal absorption from soil was in rats, in which a lower fractional absorption of 9.2% was estimated after 4-day exposure (Yang et al., 1989). Although higher organic content of the soil used could be a factor in the lower ABS in rats, the presence of petroleum crude oil (1 percent (w/w)) as a co-contaminant was also likely a factor in the lower absorption in rats compared to monkeys. Stroo et al. (2005a) note that tar in contaminated soils tends to bind hydrocarbons more tightly than conventional soil organic matter and reduces bioavailability for dermal absorption. In addition, a soil loading of 9 mg/cm^2 exceeds monolayer coverage with soil sieved to <150 µm causing a further reduction in the percent fractional absorption.

Wester et al. (1990b) observed a roughly 10-fold lower fractional absorption of BaP in human skin in vitro compared to the human in vitro study by Moody et al. (2007). Use of a course soil fraction (180-320 µm) by Wester et al. may have reduced dermal absorption. The reduction in absorption may also be due, in part, to loss of skin viability. The Wester study used cadaver skin up to 5 days after harvest. The studies of Moody et al. obtained human skin in as little as 2-24 hrs after live donor skin harvest.

The metabolic viability of the skin samples used for in vitro studies is a factor that can affect skin permeation of BaP. Kao et al. (1985) have shown that the rate of cutaneous metabolism of BaP has a positive correlation with the permeation rate of BaP through viable skin. For example, using previously frozen human skin, as was done in some studies discussed above, renders the samples less viable and possibly much less permeable to BaP. When BaP was applied in vitro to fresh skin samples and previously frozen skin from the same individuals, a significant reduction in dermal absorption into the receiver solution was observed for the previously frozen skin (Moody et al., 2009a). However, when the skin depot was included, the difference in dermal absorption between fresh and previously frozen skin was not as pronounced.

The dermal exposure algorithm presented in Chapter 6 includes a half-life variable for BaP in soil, although it is generally assumed the half-life reflects primarily the loss of chemical due to microbial degradation. However, Adbel-Rahman et al. (2002) showed that aging of BaP in sterile soil also resulted in decreased fractional absorption in pig skin. This finding suggests BaP also shows reduced bioaccessibility over time due to partitioning into more remote sites within the soil matrix. Vigorous soil extraction procedures often used to assess soil half-life may overestimate the bioavailability of BaP because it may not be a true representation of BaP's bioaccessibility in soil for dermal absorption. Extraction techniques using human sweat or synthetic sweat would provide a more accurate estimate of the BaP half-life in soil for fractional dermal absorption studies.

F.4.4 Hexachlorobenzene

Recommended use of default organic compound ABS estimate of 4%

F.4.4.1 Studies Considered

No experimental data are available investigating the dermal absorption of HCB from contaminated soil. In a rat in vivo study, ^{14}C-HCB dissolved in tetrachloroethylene was applied neat to the skin and covered with an occlusive patch after the vehicle had evaporated (Koizumi, 1991). The cumulative mean absorbed body burden, not including dosed skin directly contaminated, was 2.67% after 24 hours. Approximately 5% of the total dose remained in or on the dosed area of skin prior to washing. Washing the dosed area of skin resulted in

removal of 4% of the total dose, indicating that 1% of the total dose was absorbed in the skin on which ^{14}C-HCB was directly applied.

A Monte Carlo simulation was developed to produce a probability density function for the dermal uptake fraction of HCB in soil deposited on human skin (McKone, 1991). A two-layer model was used that accounted for chemical properties, skin properties, soil properties, and exposure conditions. The resulting modeled daily dermal uptake fraction had an arithmetic mean value of 0.15 per day (24 hrs), and an arithmetic standard deviation of 0.18 per day.

F.4.4.2 Discussion and Recommendation for a Hexachlorobenzene Compound ABS

A single dermal absorption study in rats observed a 24-hr fractional absorption of 4% (rounded to nearest whole number) for the neat compound. This estimate includes HCB retained in skin at the site of application. Absorption of HCB may have increased as a result of occlusion of the exposed skin area to prevent evaporation of HCB.

A default ABS of 4% is recommended based on the rat dermal exposure study, although the chemical was applied neat to the skin. An HCB modeling study suggests that the fractional absorption of HCB in soil may be 15%, so no adjustment was made to the ABS to account for reduced absorption due to partitioning to soil organic matter (McKone, 1991). In support, HCB is structurally similar to hexachlorocyclohexane (HCH), which has an ABS of 3%. However, the K_{ow} for HCB (log K_{ow} 5.73) is about 100 times greater than that of the HCHs, which would suggest a greater ability for absorption into skin. On the other hand, the high K_{ow} also indicates that HCB will have stronger sorption to soil organic material compared to the HCHs, which usually decreases the dermal absorption potential. Until more relevant dermal absorption studies are conducted, an ABS of 4% is recommended for HCB.

F.4.5 Hexachlorocyclohexanes

Hexachlorocyclohexanes (HCHs) occur as eight isomers. The most common isomer is the gamma, which when purified to 99%, was sold under the trade name of lindane. Lindane was a widely used pesticide but almost all uses of lindane have been banned in the United States due to carcinogenicity concerns, high biopersistence and bioaccumulation. Dermal absorption data exist only for lindane, thus all HCH isomers are considered to have the same dermal absorption characteristics as lindane.

Recommended point estimate for dermal uptake from soil: 3%

F.4.5.1 Studies Considered

A Key Study

The only study located regarding dermal absorption of HCHs from soil was that of Duff and Kissel (1996) who conducted in vitro dermal absorption studies using human full-thickness skin and two lindane-contaminated soils. The organic content of the sieved sub-150 µm soils were 3.87% (sandy loam) and 0.73% (silt loam). The lindane-spiked soils were stored for up to 19 days prior to testing. No effect of aging was observed within this time frame. The studies were carried out for 24 hours with soil loading at 1, 5 or 10 mg/cm^2. The relative percent absorption decreased significantly with soil loads of 5 and 10 mg/cm^2. This was attributed to monolayer coverage of skin occurring at about 2 mg/cm^2, resulting in reduced fractional absorption at the higher soil loadings.

Results of this study showed that most of the mass of absorbed lindane was found in the skin. The average fraction of total dermal uptake found in the receptor fluid for both soils was only about 4%. Mean 24-hour total dermal absorption values (found in receptor fluid + skin) at a soil load of 1 mg/cm^2 was 1.96 and 2.35%, for low and high organic content soil, respectively. Approximately 40% of the lindane was lost to volatilization with a soil load of 1 mg/cm^2, while significantly lesser amounts were lost in the higher loading trials (less than 10% for the sandy loam soil at 10 mg/cm^2; less than 20% for the silt loam soil at 10 mg/cm^2).

B Supporting Studies

Feldman and Maibach (1974) examined the percutaneous absorption of lindane dissolved in acetone and applied to the skin of human subjects (n = 6). Radiolabeled lindane (4 µg/cm^2) was applied to ventral forearm skin and the urinary excretion of ^{14}C was measured for 5 days after the single topical application. The skin sites were not protected and subjects were asked not to wash the area for 24 hours. Data obtained after i.v. dosing were used to correct the skin penetration data for incomplete urinary recovery. Results indicate that 9.3% (SD 3.7) of the dose was absorbed. However, when skin was occluded, the percent of absorbed dose increased dramatically to 82.1%.

In another human study, lindane was dissolved in acetone and applied to the ventral forearm of volunteers and covered with a nonocclusive patch (Dick et al., 1997a). Six hours after application approximately 80% of the applied lindane dose (120 mg lindane per ml acetone) had not been absorbed and 14% of the dose was found in the stratum corneum (measured by tape-stripping). The authors conclude that 5% of the applied dose was absorbed to the systemic circulation by 6 hours. Although the disappearance method was used to estimate systemic absorption, measurable levels of lindane were found in the bloodstream and lindane metabolites were found in the urine. By 24 hours, tape stripping of the remaining volunteers showed the stratum corneum contained

very little of the applied lindane and only about 0.01% of the dose had been lost through desquamation, suggesting that nearly all the lindane detected in the stratum corneum at 6 hours had been systemically absorbed or absorbed into deeper skin layers by 24 hrs.

F.4.5.2 Discussion and Recommendation for a Hexachlorocyclohexane ABS

Although only one study for dermal absorption of lindane from soil is available, the findings provided consistent results for a human in vitro fractional absorption range of 0.45 to 2.35% under different soil loadings and soil types (Duff and Kissel, 1996). The highest fractional absorption of 2.35% was chosen as the basis for the HCH ABS, given that the soil loading (1 mg/cm^2) used was the only one that was at or below monolayer skin coverage. An average of only 4% of the absorbed dose (approximately 0.09% of the applied dose) was found in the receptor fluid after 24 hrs. However, in vivo studies show extensive absorption of lindane into all skin layers, with continued absorption of lindane beyond the stratum corneum 6 hrs after removal of lindane from the skin surface (Dick et al., 1997a). Thus, lindane retained in skin depots should be presumed to be available for eventual systemic absorption.

Duff and Kissel (1996) noted the unexpected result that the soil with the higher organic carbon content generated a higher fractional absorption (2.35%) than the soil with low organic carbon content (1.96%) at equivalent soil loadings of 1 mg/cm^2. Increasing organic carbon content of soil generally reduces transport, and dermal absorption, of organic compounds in soil. The authors theorized that this inconsistent finding at 1 mg/cm^2 was due to inter-individual differences in skin absorption, which would not have occurred had the same skin donors been used for both soils.

To account for known effects of organic content of soil the ABS of 2.35% is rounded up, rather than down, to one significant figure for a final ABS of 3%. In support of this ABS adjustment, soil loadings of 5 and 10 mg/cm^2 from high organic content soil did reduce fractional absorption of lindane compared to lindane in soil with low organic content (Duff and Kissel, 1996). However, monolayer coverage of skin was exceeded at these higher soil loads, resulting in lower fractional absorption compared to fractional absorption at 1 mg/cm^2.

Other data available on percutaneous absorption of lindane or other HCH isomers, which are obtained from studies that use acetone or topical creams and lotions as the vehicle, are not relevant for estimating fractional absorption of lindane from soil (Franz et al., 1996). Use of topical creams and lotions as a vehicle for lindane in dermal absorption studies is related to lindane's use as a medicine to treat scabies.

Theoretical calculations in which release from soil is not the primary limiting factor in the dermal absorption of lindane predict the percent absorbed at 55.6 to 98.5% (Bunge and Parks, 1997). The upper end of this range brackets the

82.1% absorption of applied dose observed by Feldman and Maibach (1974) when the vehicle is acetone and evaporation of lindane is limited by occlusion. However, the lower dermal absorption of lindane from soil observed by Duff and Kissel (1996) is consistent with the theory of slow soil release kinetics, in which partitioning from soil to skin is the limiting factor in dermal absorption for a number of organic compounds (Bunge and Parks, 1997). Oral bioavailability data for absorption of lindane from soil support the dermal data for absorption of lindane from soil. Soil (organic matter content of 9.8%) spiked with lindane and aged was found to have an oral bioavailability of only 7.2% in an in vitro gastrointestinal extraction test (Scott and Dean, 2005).

The dermal exposure scenario used in this document assumes that deposition of contaminated soil occurs on non-occluded skin exposed to the environment. These conditions would promote evaporation of lindane from soil on the skin, resulting in less absorption into skin than might be expected (Wester and Maibach, 1985; Duff and Kissel, 1996). A potential limitation of this ABS is if significant dermal deposition of lindane-contaminated soil occurs on skin under clothing. The situation may then become one of a reservoir for lindane in which enhanced dermal absorption occurs because of limited evaporation. However, the volatilization potential for lindane from soil also suggests that the absorption potential for lindane may be more significant when exposure is from excavated soils or from surface soils soon after the contamination event (Bunge and Parks, 1997). These various countervailing influences on dermal absorption of lindane under the exposure scenario support the assumption that the ABS will not underestimate actual dermal absorption.

F.4.6 Diethylhexylphthalate (DEHP)

Recommend point estimate for dermal uptake from soil: 9%

F.4.6.1 Studies Considered

A Key Studies

No studies were located on dermal absorption of di(2-ethylhexyl)phthalate (DEHP) from soil.

Deisinger et al. (1998) estimated the migration and subsequent absorption of radiolabeled DEHP from polyvinyl chloride film into rat skin in vivo. Based on the amount of DEHP that migrated from film (505.6 mg) with 24 hr dermal exposure, systemic absorption was estimated at 3.4% of the migrated dose. After skin washing, the residual fraction in skin at the site of dermal application was 13.8% of the migrated dose. Assuming the fraction of DEHP in skin will be eventually absorbed systemically, a maximum absorption rate of 0.24 µg/cm^2/hr was calculated.

Barber et al. (1992) carried out an in vitro DEHP dermal exposure study to compare rates of absorption through full thickness rat skin and human stratum

corneum. DEHP was applied to skin samples in saline solution, and absorption expressed in terms of absorption rate after 32 hrs of exposure. Absorption through rat skin and human stratum corneum was 0.42 and 0.10 μg/cm^2/hr, respectively, indicating that DEHP more rapidly penetrated rat skin than human stratum corneum by a factor of 4.2.

Damage to the rat skin observed following exposure was implied as a possible reason for greater permeability of DEHP through rat skin. Scott et al. (1987) compared absorption rates of DEHP through rat and human epidermal membranes (dermal layer removed), obtaining rates of 2.24 and 1.06 μg/cm^2/hr for rat and human skin, respectively. DEHP was applied to the skin sample in 50% v/v aqueous ethanol with exposure up to 53 hrs for rat skin and 72 hrs for human skin. Damage to rat skin, but not human skin, was also observed by Scott et al. (1987) after exposure.

B Supporting Studies

The National Toxicology Program investigated the dermal absorption of ^{14}C-labeled DEHP in male F344 rats (Melnick et al., 1987; Elsisi et al., 1989). The labeled compound was dissolved in ethanol and applied directly to the skin (30 mg DEHP/kg body weight; n = 3 per time point) at a dose of 5-8 mg/cm^2. The ethanol was then evaporated and the site of application was covered with a perforated plastic cap. DEHP showed a very slow rate of excretion over five days, likely reflecting a slow dermal uptake process. After five days, approximately 86% of the applied dose was recovered from the skin at the site of application. However, it was not determined how much of the applied dose remained on the surface of the skin and how much was absorbed into the skin. Approximately 5% of the applied dose was recovered in urine and feces, while the amount of the label remaining in the body five days after dosing was less than 2% of the applied dose of DEHP.

Ng et al. (1992) examined dermal absorption of DEHP both in vivo and vitro in hairless guinea pigs. In an in vivo study, radiolabeled DEHP dissolved in acetone (53 μg DEHP; 34 nmols/cm^2) was applied topically on a dorsal area of the animals which was then covered with a nonocclusive patch. After 24 hours, the patch was removed and the dosing site cleaned to remove any unabsorbed compound. Absorption (estimated from urine and feces) was monitored up to 7 days post treatment. To account for incomplete excretion after the compound was absorbed, a dose of ^{14}C-DEHP was given intramuscularly to a group of animals (n=5) and radioactivity was measured in urine and feces for up to seven days.

After 24 hours, 3% (7% after correction) of the dermally applied dose was eliminated in urine and feces. After seven days, approximately 21% (53% after correction) of the dose had been absorbed by the skin and eliminated, while another 11.3% of the dose had been skin stripped from the dose area. An additional group (n=6) of animals was given DEHP (53 μg) dermally to estimate

the dose remaining in the tissues. After 7 days, ^{14}C content (% of applied dose) was as follows: urine, 18 ± 4; feces, 4 ± 1; skin wash after 24 hrs, 32 ± 10; skin patch, 13 ± 5; skin (dosed area), 5 ± 3; other tissues (liver, fat, muscle, skin), 4 ± 3%. An additional 10% was estimated to be lost to volatilization.

In the in vitro study, Ng et al. (1992) examined absorption of DEHP through viable and non-viable dermatomed guinea pig skin (200 µm sections) with 24-hr exposure. Radiolabeled DEHP was applied in 10 µl acetone at concentrations of 35.6, 153, or 313 nmol/cm^2. The percentage of dose that permeated the viable skin into the receptor fluid was 6, 2.4, and 2.5% for the low-, medium-, and high-dose groups, respectively. The percentage of dose that remained in the skin disc was 41.0, 37.5, and 36.2% for the low-, medium-, and high-dose groups, respectively. Use of nonviable skin resulted in a slightly decreased penetration of 5.0% at the applied dose of 35.6 nmol/cm^2, likely due to decreased metabolism of DEHP. There was a dose-related increase in metabolism but the total metabolites were between 0.5 and 1% of the applied dose for each dose group.

Chu et al. (1996) examined the skin reservoir effects of ^{14}C-labelled DEHP (119-529 µg/cm^2) applied on hairless guinea pigs for 24 hrs, followed by washing of the skin to remove DEHP and analysis of DEHP distribution up to 14 days post-treatment. As DEHP in the dosed skin decreased from 11.1% to 0.66% from 24-hrs to 7 days post-treatment, excreted DEHP gradually increased from 0.74 to 17.3%.

This finding provided evidence that DEHP stored in skin enters the systemic circulation, although the considerable intraspecies variation for percent of absorbed dose precluded a specific estimate of DEHP absorbed systemically after 24 hrs post-treatment. DEHP in the carcass was 1.01 and 0.92% of applied dose at 24 hrs and 7 days, respectively. By 14 days post-treatment, essentially no DEHP remained in dosed skin. Autoradiographic analysis of the dosed skin at 24 hrs revealed dense radiolabel accumulation in the epidermis and along the hair follicles, which indicated hair follicles may be a penetration pathway for DEHP.

The authors also reported that the percent absorbed at 24 hours by Ng et al. (1992) was higher than that found in this study, with nearly identical experimental protocols. They attributed this difference to the higher doses used in the present study (10 times higher when expressed in µg/cm^2) stating that saturation might have occurred at higher doses, resulting in a lower fractional absorption.

F.4.6.2 Discussion and Recommendation for a Diethylhexylphthalate ABS

Although two in vitro dermal absorption studies have been carried out with pure DEHP on human skin, data were not provided to determine ABS values. However, absorption rates were determined for both rat and human skin under similar exposure conditions and compared. The DEHP absorption rate for

humans was 2-4 times less than that for rats (Scott et al., 1987; Barber et al., 1992).

In vivo studies in rats and guinea pigs that determined absorption of DEHP by total mass balance provide the best estimates for fractional dermal absorption in these species. Deisinger et al. (1998) used PVC film as the vehicle for transfer of DEHP to the skin of rats. Using PVC film as the vehicle will slow absorption, as DEHP requires transfer from the film before partitioning into skin can occur. This type of chemical transfer may give a closer estimate of a DEHP ABS from soil, compared to skin application of the pure compound as performed by the other studies. Including both systemic absorption and compound in skin at the site of application, a fractional dermal absorption value of 17.2% is attained from the Deisinger study. The rat-to-human absorption rate ratio of 2.1 determined by Scott et al. (1987) is then applied to give a final ABS of 9% (rounded up from 8.6%).

DEHP in the skin is included in this estimate, as Ng et al. (1992) and Chu et al. (1996) found there is significant systemic absorption of DEHP in skin up to 7 or more days after removal of DEHP from the skin surface. For this reason, the rat study by Melnick et al. (1987) was not considered in this assessment. The Melnick study did not wash DEHP off the site of skin application prior to analysis, so it is unknown how much DEHP was on or retained in the skin at the end of the 5 day exposure.

Similar to rats, Chu et al. (1996) also noted that guinea pig skin is considered generally more permeable to chemicals than human skin. Thus, it is not unexpected that the rat ABS of 17.2% is within the range of 9.5 to 18.9% (DEHP systemically absorbed + DEHP in skin) determined by the authors in guinea pigs. A limitation for this ABS is that both Ng et al. (1992) and Chu et al. (1996) reported that the percent absorbed in guinea pigs appeared to be higher at low application concentrations, although nearly identical experimental protocols were used. They attributed this difference to possible skin saturation occurring at higher doses (about 119-529 $\mu g/cm^2$), resulting in a lower fractional absorption. If saturation of DEHP in rat skin has occurred in the Deisinger et al. (1998) study, this may result in an underestimation of the fractional absorption value at soil concentrations associated with airborne releases.

Another limitation includes reliance on studies in which DEHP is applied directly onto the skin (i.e., neat), rather than combined with soil, for estimation of fractional dermal absorption. Kissel (2011) has reported that fractional absorption is dependent on skin loading conditions for application of organic chemicals directly to skin. Increased skin loading of an organic chemical will result in lower fractional absorption provided complete coverage of the skin at the site of application occurs. Using PVC film as a surrogate for soil for transfer of DEHP from the film to skin is used in the estimation of the ABS, and thus reduces potential mismeasure of dermal absorption of organic compounds applied neat.

Other limitations include lack of data for dermal absorption of the compound bound to soil was located in the literature. In addition, no oral bioavailability studies for DEHP bound to soil could be found. Thus, no further adjustment of the ABS for absorption from a soil was applied.

F.4.7 Dermal Absorption Fraction for 4,4' –Methylenedianiline

Recommended use of default organic compound ABS estimate of 10%.

F.4.7.1 Studies Considered

Brunmark et al. (1995) utilized a patch-test method to evaluate dermal exposure and pharmacokinetics of 4,4'-methylene dianiline (MDA) dissolved in isopropanol. Measurements of MDA were made in plasma and urine of the five human volunteers. The extent of absorption was evaluated by measuring the amount remaining in the patch after 1 hour. Determination of MDA remaining in the patch showed 25 to 29% was absorbed. The authors also describe elimination half-lives from plasma and urine.

Workers were monitored for two consecutive weeks in a fiber glass pipe factory for dermal exposure to MDA (diluted with triethyleneamine) using both cotton glove and hand wash monitoring (Brouwer et al., 1998). Urinary excretion of methylene dianiline was also evaluated. Urinary MDA levels correlated well with exposure measurements. Geometric means of daily exposure ranged from 81 to 1783 μg MDA, while 24 hour urine samples ranged from 8 to 249 μg MDA. Given that the Brunmark study identified a urinary half-life of MDA of 7 hours and that the measurements on the hands and forearms of the workers correlated strongly (0.94) with the urinary excretion of MDA, one can roughly estimate that between 10 and 14% of the MDA on the hands and forearms was absorbed by the workers.

MDA was applied in vitro to unoccluded human and rat skin for 72 hrs at a loading of 17.7-40.6 μg/cm^2 in ethanol (Hotchkiss et al., 1993). Absorption into the receptor fluid at 72 hrs was 6.1 and 13.0% of the applied dose for rat and human skin, respectively. When the skin was occluded, the absorption at 72 hrs was significantly enhanced, reaching 13.3 and 32.9% for rat and human skin, respectively. MDA that remained in human skin at 72 hrs was 23.8 and 37.4% of the applied dose for unoccluded and occluded skin, respectively. For the rat, MDA content of the skin at 72 hrs was 57.6 and 53.1% of the applied dose for unoccluded and occluded skin, respectively. Although the data were only graphically presented, absorption through human skin into the receptor fluid at 24 hrs can be estimated at 8% of the applied dose for unoccluded skin and 20% of the applied dose for occluded skin.

The permeability of rat and human skin in vitro to MDA was assessed by Kenyon et al. (2004) over a large dose range, and the potential for skin to act as a reservoir for MDA was investigated. Dose levels of 0.01, 0.1 and 1 mg per 0.32

cm^2 skin were applied in ethanol:water (50:50) onto occluded skin for 24 hrs. No statistical difference in skin permeability was observed between rat and human skin. After 24 hrs, 27 to 52% of applied MDA had penetrated human skin to the receptor fluid. The percentage of applied MDA retained in human skin was 20%.

In another in vitro experiment, Kenyon et al. (2004) applied 0.1 mg MDA to human skin for 4 hrs, then removed excess MDA on the skin surface and the experiment continued for another 4 hrs. The cumulative absorption rate of MDA into the receptor fluid remained the same for the last 4 hrs, with only a slight decrease noted between 7 and 8 hrs. Of the total 11% of the MDA found in the skin, 5% was removed by tape stripping the stratum corneum. The remaining 6% of MDA was found in the digested skin, suggesting this amount would have been absorbed had the experiment continued longer. Considering that the lag time for appearance of MDA in receptor fluid was about 4 hrs, the authors presumed that the MDA remaining in the stratum corneum at 8 hrs would not be absorbed systemically.

No literature could be located regarding dermal absorption of MDA from soil. However, the fate of MDA added to soil has been investigated. MDA rapidly and strongly absorbs to loam soil which contained a total organic content of 1.3% (Cowen et al., 1998). However, MDA does not appear to form complexes with humic materials or form other irreversible soil binding processes. In one year, the aerobic biodegradation of MDA in silt loam soil was 40%.

F.4.7.2 Discussion and Recommendation for a 4,4'–Methylenedianiline ABS

Dermal absorption of MDA in workers is considered a more significant route of exposure than inhalation (Brouwer et al., 1998). The in vivo worker data support the in vitro human data in that dermal absorption is considerable. However, the exposure/application of MDA involved other organic solvents. The effect of solvent vehicle on absorption was not investigated.

No data could be located regarding dermal or oral absorption of MDA bound to soil. In addition, no oral bioavailability studies for MDA bound to soil could be located. Soil fate studies indicate that MDA binds strongly to soil, which would likely reduce dermal absorption considerably, and biodegrades slowly over a year's time. Thus, the default absorption value of 10% for organic compounds is recommended until soil-bound dermal studies are available.

F.5 Comparison with Other Published Dermal Absorption Factors

Two other agencies have published fractional dermal absorption estimates for some of the Hot Spots chemicals presented in this document. These values are shown in Table F.5 and are compared with the fractional dermal absorption values developed by OEHHA.

Table F.5. Published Point Estimates and Default Dermal Absorption Factors (ABS) as Percent of Selected Chemicals from Soil

CHEMICAL	ABS (percent)		
	OEHHA[a]	US EPA[b]	DTSC[c]
Inorganic chemicals			
Arsenic	6	3	3
Beryllium	3	[d]	[e]
Cadmium	0.2	0.1	0.1
Chromium (VI)	2	[d]	[f]
Fluoride	3	[d]	[e]
Lead	3	[d]	[e]
Mercury	4	[d]	[e]
Nickel	2	[d]	[e]
Selenium	3	[d]	[e]
Organic chemicals			
Di(2-ethylhexyl)phthalate (DEHP)	9	[g]	[g]
Hexachlorobenzene	4	[g]	[g]
Hexachlorocyclohexanes (as lindane)	3	[g]	[g]
4,4'methylene dianiline (MDA)	10	[g]	[g]
Pentachlorophenol	[h]	[g]	[g]
Polychlorinated biphenyls (PCBs)	14	14	15
Polychlorinated dibenzo-p-dioxins and dibenzofurans (as TCDD)	[h] 3	[g] 3, 0.1[i]	[g] 3
Polycyclic aromatic hydrocarbons	13	13	15

[a] ABS values, as presented in this document by OEHHA. In most cases, the OEHHA ABS represent dermal absorption values based on the soil vehicle freshly spiked with the chemical contaminant and placed on skin for up to 24 hrs.
[b] (U.S. EPA, 2004) [c] (DTSC, 1994)
[d] An ABS point estimate is not specifically listed for this chemical. For inorganics with insufficient data, USEPA (2004) states that the speciation of the compound is critical to the dermal absorption and there are too little data to extrapolate a reasonable default value.
[e] California's Department of Toxic Substances Control (DTSC, 1994) recommends using 1% as the default dermal absorption value for metals, based on Clement Associates (1988).
[f] California's Department of Toxic Substances Control (DTSC, 1994) in their Preliminary Endangerment Assessment Guidance Manual does not recommend a fractional absorption value for Cr(VI) due to lack of systemic carcinogenicity via non-inhalation routes of exposure.
[g] No specific default ABS value is listed [h] To be assessed for dermal absorption
[i] USEPA (2004) recommends a dermal absorption fraction from soil of 3%, or a dermal absorption fraction of 0.1% if the soil organic content is > 10%.

F.6. References

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