Human Health Risk Assessment

Appendix 7

Dermal Uptake Coefficients for Metals

Table of Contents
Human Health Risk Assessment - Appendix 7
Dermal Uptake Coefficients for Metals

A7-1 Dermal Uptake Coefficients for Metals

Daily contact with metals through soil present on the skin represents a potential route of exposure. However, the insoluble nature of most metals in soil limits their bioaccessability for uptake into and through the skin. Where data is available, it shows that dermal uptake of metals is low (Paustenbach, 2000). The rate at which a metal is taken up into the outer layers of the skin is referred to as the *dermal uptake coefficient* (DUC). Studies of the dermal absorption of nickel have suggested that the outer layer of the skin, the stratum corneum, can act as a collector for dermally applied nickel before it enters the underlying tissue (Fullerton et al., 1992). While there is little information available in the scientific literature on dermal uptake of the other metals of concern in this assessment, it is reasonable to assume that similar mechanisms will govern their absorption into the body. This process can be considered to be equivalent to ingestion or inhalation intakes where the material is delivered into the gut or lungs, but cannot be considered to have entered the body proper until it is absorbed through the gut or lung lining and into the underlying tissue or blood.

Therefore, for the purposes of this assessment, dermal uptake coefficients will be used to estimate the amount of each metal that could be delivered to the skin through contact with soil (referred to as *Dermal Intake*). The calculation of dermal intakes for each metal is provided in Appendix 3.

Dermal absorption studies typically use exposure periods extending well past 24 hours. However, the amount of time a human receptor is in contact with a chemical/soil mixture on the skin should correspond with soil contact times normally encountered (US EPA, 1992). In real life situations, soil is likely to remain in contact with the skin for only a few hours. Consequently, dermal intake estimates from studies with longer than 24 hours are likely to overestimate normal human exposures.

Metal specific dermal uptake coefficients have been identified for two of the six metals (cobalt and nickel) considered in the detailed exposure assessment. The selection of the dermal uptake coefficient for each metal is discussed below.

A7-2 Dermal Uptake Coefficient for Nickel

Studies of how nickel can penetrate the skin in humans and animals are limited. Only studies of intact organisms where nickel is measured in blood or urine can show whether nickel has penetrated through the skin layers into the bloodstream. This is important since permeation of nickel into the upper layers of the skin does not automatically mean that nickel has been absorbed into the body. Similarly, contact dermatitis reactions following dermal application of nickel solutions may not imply complete penetration but only irritation of the deep layers of the skin. There are few studies that address the uptake of nickel through human skin available in the literature. Human studies may be separated into application of nickel to intact skin in individuals

(Norgaard; 1955, 1957), and, *in vitro* studies with excised human skin in diffusion cells (Fullerton et al., 1986; 1992, Frankild et al., 1995, Samitz and Katz, 1976). In addition, reviews are available (ATSDR, 1997, Hostynek et al., 1993). The available studies on nickel uptake in human skin have focused primarily on the uptake of nickel and its relationship with nickel contact dermatitis (Norgaard, 1955; Fullerton et al., 1986; 1992; Frankild et al., 1995; Samitz and Katz, 1976).

A7-3 Intact Skin Studies

These studies have examined the uptake of soluble forms of nickel into the outer layers of the skin. Two types of study protocols are used to measure dermal uptake; studies where nickel compounds were applied to skin and secured with some form of patch occluding the skin and studies where the applied material were not secured with a patch. Norgaard (1955) applied aliquots of radioactive ^{57}Ni to the forearm. This area was occluded and the radioactivity measured by placing the counter directly over the treated area. Loss of radioactivity with time was interpreted as resorption through the skin, however, no measures of radioactivity in blood or urine were taken. On this basis, dermal uptake rates that ranged between 55% and 77% over a 24 hour period when nickel sulphate was applied to occluded skin reported (Norgaard, 1955). However, it could not be determined if the nickel in this study was actually bound in the outer layers of the skin (ATSDR, 1997). This limits the utility of the study for assessing dermal absorption of nickel compounds.

A7-4 *In vitro* Studies of Excised Skin

Nickel diffusion through excised cadaver skin was studied using ^{63}Ni (as nickel sulphate) (Samitz and Katz, 1976). The diffusion of nickel (0.001M to 0.1M) from physiological saline or human sweat through the epidermis was slight. However, considerable amounts of nickel were bound to the epidermis. No diffusion of nickel through the epidermis took place within five hours, even after 48 hours, less than 0.1% of the nickel diffused through the skin. The excised epidermis does not seem to have been occluded.

In a study that applied nickel chloride to excised human skin, Fullerton et al., (1986) reported that 0.23% of the applied dose was absorbed over a 144 hour period in unoccluded skin while 3.5% was absorbed by occluded skin. In a follow-up study designed to determine the efficacy of different vehicle carriers for dermal patch testing, Fullerton et al., (1992) reported that dermal uptake of nickel sulphate in excised human skin, ranged between 3% and 5% of the applied dose in occluded skin over a 93 hour testing period. The study further showed that the level of absorption was dependent on the carrier vehicle used, and that the dermal absorption of dissolved nickel was greater than that of undissolved or crystalline nickel (Fullerton et al., 1992). Analysis of nickel levels in the stratum corneum, epidermal, and dermal layers of skin also showed that the outer stratum corneum layer held the highest levels of nickel. The study also found that little nickel was able to penetrate through all layers of the skin to the underlying tissue (Fullerton et al., 1992). The authors suggest that this layer of the skin may act as a reservoir for nickel that could allow nickel to move into other tissue and that as the level of nickel increases in this layer, subsequent exposures would allow greater amounts of nickel to move through the skin (Fullerton et al., 1992).

Frankild et al., (1995) examined the time- and dose-related effect of the detergent, sodium lauryl sulphate (SLS), on *in vitro* percutaneous penetration of radio labeled ^{63}Ni chloride in excised human cadaver skin. Simultaneous application of SLS (0.25%, 2% and 10%) and nickel chloride resulted in a significant dose response relationship between SLS concentration and penetration of nickel. Inspection of the data indicates that as in the studies reported by Fullerton et al., (1986, 1992), no penetration occurred over the first 48 hours of the experiments, and all the SLS-mediated penetration occurred after 48 hours. No penetration of nickel chloride occurred in the SLS free controls (Frankild et al., 1995).

This information suggests that while soluble nickel may accumulate in the upper layers of the skin in the initial 48 hours, penetration, if any, does not occur until later. In the context of nickel in soil in contact with the skin for periods of less than 24 hours, assuming normal hygiene, it is difficult to make a case for any dermal penetration of nickel. Consequently, prorating dermal penetration rates based on cumulative penetration after 69 hours or 96 hours *in vitro* exposures will overestimate dermal nickel intake estimates. As pointed out by Frankild et al., (1995), *in vitro* skin models are limited in that the metabolic pathways of the skin and normal repair mechanisms are not functioning.

It should be stressed that the work of Fullerton et al., in 1992 was conducted with occluded skin. This is not representative of dermal contact with soil where exposures would not be expected to last for more than 24 hours. Further, Hostynek et al., (1993) note that occlusion increases skin penetration ten fold over unoccluded conditions. The authors further note that sweat contains significantly higher levels of nickel than normal blood serum and that it is a significant excretory pathway for the metal (Hostynek et al., 1993). Thus, it would appear that dermal absorption of nickel from soil is likely to be very limited and that much of what is absorbed into the outer layers of the skin is likely to be lost from the skin due either to removal in sweat or through the normal loss of outer skin cells from the stratum corneum.

The study using unoccluded skin most closely resembles the dermal exposures to nickel in soil that could be expected in the Rodney Street community. Therefore, the absorption factor of 0.23%, reported by Fullerton, et al., (1986) was used to develop a dermal uptake coefficient for nickel in Port Colborne.

As noted above, Fullerton et al., 1986 reported that 0.23% (0.0023) of an applied dose of nickel chloride was absorbed over a period of 144 hours. However, bathing activities can be expected to limit skin contact with nickel bearing soil to a maximum of 24 hours. Therefore, it is necessary to correct the uptake coefficient reported by Fullerton et al., (1986) to account for the difference in the expected exposure duration of 24 hours and the 144 hours used in the Fullerton study. In developing a corrected dermal uptake coefficient for nickel oxide, it has been assumed that soil would remain in contact with the skin for a period of 24 hours before being removed by bathing activities. The derivation of dermal uptake coefficient for nickel is shown in equation A7-1.

Eq A7-1:

$$DUC_{Ni} = 0.0023 * \left(\frac{24 hours}{144 hours} \right) = 0.00038 = 3.8 X 10^{-4}$$

Where:

DUC_{Ni} = Dermal Uptake Coefficient for nickel
24 hrs = Expected exposure duration
144 hrs = Duration of experimental exposure
0.0023 = Reported dermal absorption of Nickel Chloride

It should be noted that this approach assumes a linear relationship between the length of exposure and the amount of nickel available to the skin for absorption. It should also be noted that there is a marked difference in water solubilities between the nickel chloride used by Fullerton et al., (1986) and nickel oxide which is the predominant form of nickel found in the soil on Rodney Street and elsewhere in Port Colborne. Reported solubilities are 642 g/L and 0.0011 g/L for nickel chloride and nickel oxide respectively (ATSDR, 1997). Further, the nickel chloride used by Fullerton et al., (1986) was applied in solution and was freely available for absorption by the skin. In Port Colborne, the nickel oxide is associated with soil particles and must dissociate (dissolve) from the soil particles before it is available for absorption by the skin. Therefore, using a dermal dose factor derived for dissolved nickel chloride to estimate the dermal dose of undissolved nickel oxide, will significantly overestimate the amount of nickel oxide available for absorption by the skin. Thus, the DUC_{Ni} factor selected for use at Rodney Street in Port Colborne will provide conservative estimates of dermal exposure for all age groups considered in the assessment.

A7-4.1 Dermal Bioaccessibility

For the NiO in the soil to become available for penetration through the layers of the skin, the nickel has to be in a soluble form. The nickel oxide in the soil may dissolve to some degree in the layer of sweat on the skin during perspiration. The soluble nickel speciation data from the Lakefield testing (Part A, Table 10) may not be equivalent to extraction in synthetic sweat but may indicate some estimate of the soluble nickel available to penetrate the skin. The soluble nickel leaching approach used by Lakefield extracted the soil samples in hot water for 30 minutes. Soil pH (Part A, Table 9) ranged from pH 6.85 to pH 7.75, however, while the pH of the hot water extracts was not reported, it is not expected to be much below pH 7. Hot water was used instead of the 0.1 M ammonium citrate (pH 4.4) used by Zatka et al., (1992), a fluid that is similar to artificial sweat solutions used in other studies because the hot water extraction gave a more accurate extraction of soluble nickel salts. Freshly perspired sweat has a neutral pH, however, it becomes slightly acidic (pH 4 to pH 6) depending on the presence of resident skin bacteria. The mean soluble nickel value in hot water is 0.37% (range = 0.26% to 0.68%). Tests to measure plant-extractable nickel in Port Colborne soils averaged 0.22% for pH neutral mineral soils (Part A, section 6.1.3).

Inco has provided information to suggest that at pH 7 *without the glycine buffer* used by Exponent in their bioaccessibility studies (Appendix 5), nickel extractability is 1.5 %. This information (also discussed in section A2-9.2.4) suggests that despite the generally insoluble nature of the nickel compounds present in Rodney Street community soils, some soluble nickel may leach from the soil into human sweat. The data of Fullerton et al., (1986), Frankild et al., (1995) and Samitz and Katz, (1976) indicating that nickel ions do not penetrate the upper layers of human skin for at least 48 hours support the DUC factor selected for Rodney Street community soils.

A7-5 Dermal Uptake Coefficient for Cobalt

Paustenbach (2000) cites a dermal uptake coefficient of 0.0004 for cobalt chloride. Information on the cobalt species present in Rodney Street soil is not available. Therefore, it has been assumed that the dermal uptake coefficient for cobalt chloride is representative of the dermal uptake coefficient for cobalt in soil in the Rodney Street community.

A7-6 Dermal Uptake Coefficients for Antimony, Beryllium, Cadmium and Copper

Dermal uptake coefficients for the remaining metals are not available. In the absence of such values, a default value of 0.01 is recommended by the US EPA for assessing dermal exposure to inorganic compounds such as metal salts (US EPA, 1992). However, this recommendation is based on the conservative assumption that all metal delivered to the skin is available for uptake into the skin. Sweat contains many electrolytes (mainly sodium chloride, potassium and calcium salts), urea and lactic acid. The primary secretion is similar to plasma and initially would have a neutral to slightly acidic pH. Artificial sweat solutions contain high levels of NaCl (around 10%) and lactic acid (around 5%), with a pH of about 5. An adult man secretes 650 mL/day (50 to 1600 mL/day). As noted elsewhere in this report, the amount of each metal that could be released for the soils from Rodney Street, under acidic and neutral pH conditions has been assessed (Appendix 5). For all metals, maximal % bioaccessibility occurred at acid pH. Assuming a slightly acidic (pH 5) sweat layer on the skin, the bioaccessibility of these metals from soil in contact with the skin is likely to be much less than the maximal % bioaccessibility under more acidic (pH 1.5) conditions. These values represent an over estimate of the amount of each metal that could be expected to be released from the soil while in contact with skin. Therefore, the most recent default values for dermal absorption recommended by US EPA Region III (US EPA, 1995) have been used as the dermal uptake coefficients for estimating dermal exposure to these metals.

The dermal uptake coefficients used in this report are summarized in Table A7-1.

Table A7-1: Dermal Uptake Coefficients

	Antimony	Beryllium	Cadmium	Cobalt	Copper	Nickel
Coefficient	0.01	0.01	0.01	0.0004	0.01	0.00038

A7-7 References

ATSDR (Agency for Toxic Substances and Disease Registry), 1997. U.S. Department of Health and Human Services. Toxicological Profile for Nickel. Atlanta, Georgia, USA.

Frankild, S., K.E. Andersen and G.D. Nielsen. 1995. Effect of sodium lauryl sulfate (SLS) on *in vitro* percutaneous penetration of water, hydrocortisone and nickel. Contact Dermatitis. 32:338-345.

Fullerton, A., J.R. Andersen, A. Hoelgaard, T. Menne. 1986. Permeation of nickel salts through human skin *in vitro*. Contact Dermatitis. 15:173-177.

Fullerton, A. et al., 1992. Topical nickel salts: The influence of counterion and vehicle on skin permeation and patch test response. In: *Nickel and Human Health: Current Perspectives*. 1992. Eds. E. Nieboer and J.A. Nriagu. J. Wiley and Sons, Inc. pp. 211-222.

Hostynek, J.J., R.S. Hinz, C.R. Lorence, M. Price, and R.H. Guy. 1993. Metals and the skin. CRC Critical Reviews in Toxicology. 23: 171-235.

Norgaard, O. 1955. Investigation with radioactive Ni-57 into the resorption of nickel through the skin in normal and in nickel-hypersensitive persons. Acta Derm. Venereol. 35:111-117.

Norgaard, O. 1957. Investigations with radioactive nickel, cobalt and sodium on the resorption through the skin in rabbits, guinea pigs and man. Acta Derm. Venereol. 37:440-445.

Paustenbach, D.J. 2000. The practice of exposure assessment: A state-of-the-art review. J. Toxicol. Environ. Health. Part B. 3:179-291.

Samitz, M.H. and S. Katz. 1976. Nickel - epidermical interactions: diffusion and binding. Environ. Res. 11:34-39.

US EPA. 1992. Dermal Exposure Assessment: Principles and Applications. Washington, D.C. US Environmental Protection Agency. EPA/600/8-91/011B.

US EPA. 1995. U.S. Environmental Protection Agency, Region III Technical Guidance Manual Risk Assessment: Assessing Dermal Exposure from Soil. EPA/903-K-95-003.

Zatka, V.J., J.S. Warner, D. Maskery. 1992. Chemical speciation of nickel in airborne dusts: Analytical method and results of an interlaboratory test program. Environ. Sci. Tech. 26:138-144.