Port Colborne Community Action Plan (PCCAP)

Guidance Concerning Nickel Contact Dermatitis among Nickel Sensitized Individuals in the Vicinity of the Port Colborne Refinery

Draft for review – March 28, 2023

Key Guidance

- Nickel (Ni) concentrations in soils near Vale Canada's Port Colborne Refinery are elevated due to historical emissions from refinery operations between 1918 and 1984. The company accepted responsibility for the contamination and undertook the Port Colborne Community-Based Risk Assessment (CBRA). All CBRA documentation is available at http://vale.com/canada/EN/aboutvale/communities/port-colborne/CBRA/CBRA-documentation/Pages/default.aspx
- The Port Colborne Community Action Plan (PCCAP) was initiated to address certain issues that arose from the CBRA. This document is available at Vale's CBRA website.
- Nickel is one of the most common causes of allergic contact dermatitis. Individuals who are sensitized to (i.e., allergic to) nickel can experience allergic contact dermatitis reactions if exposed to enough nickel over a prolonged period of time.
- The prevalence of nickel sensitization in the general population is primarily a result of repeated dermal contact with nickel-releasing consumer products (e.g., jewelry, watches, eyeglasses, etc.) over prolonged periods of time.
- The ingestion of nickel may elicit a dermal reaction in nickel sensitized (allergic) individuals. Prolonged dermal contact with soil containing nickel and/or nickel-releasing consumer products may also elicit a dermal reaction in sensitized individuals.
- The concentration of nickel in soil that could elicit a dermal allergic reaction in sensitized individuals (via the oral route) was estimated to range from 550 to 1,200 mg/kg for organic soil and clay, respectively.
- Quantifying the soil nickel concentrations that may elicit a dermal reaction in sensitized individuals due to dermal contact is associated with a high degree of uncertainty, resulting in a very large range of nickel soil concentrations (600 to 371,000 mg/kg).
- When working with soil (gardening or other high soil contact activities) in areas near the refinery, Ni-sensitized individuals should use gloves and be fully clothed to minimize exposure.
- It is important to take steps to avoid or limit prolonged dermal contact with nickel-releasing consumer products to prevent sensitization in the first place. If a dermal allergic reaction is observed or suspected, consider consulting your health care provider.
- The Vale Port Colborne information helpline is available by telephone (289-478-8253) or email (Ontario.questions@vale.com) to have questions answered.

Contents

About this Document

This guidance document has been prepared to provide specific knowledge to Port Colborne residents regarding Ni allergic contact dermatitis. This is necessary because of the elevated soil metal concentrations (primarily Ni, Cu, Co, and As) in the vicinity of the Port Colborne Ni refinery, which operated between 1918 and 1984.

This Draft Guidance for review (dated March 28, 2023) has been provided to the Ministry of Environment, Conservation, and Parks (MECP) for comment. Vale will respond to MECP comments with a revised version of the guidance. Vale's responses to the comments will be provided as a separate document which will be referenced in the revised version. The revised guidance will be posted on Vale's Port Colborne Refinery website.

The 'Supporting Information' section is technical in nature and is provided for the purposes of transparency, presenting the calculations used to support the Key Guidance and providing some explanation of those calculations.

Comments on this guidance are always welcomed.

Supporting Information

Nickel is one of the most common causes of allergic contact dermatitis. Individuals sensitized (allergic) to nickel can experience allergic contact dermatitis reactions if exposed to enough nickel over a prolonged period of time. Oral exposure to nickel does not cause nickel sensitization. In some cases, oral exposure to nickel has been demonstrated to reduce the susceptibility to dermal nickel sensitization. The prevalence of nickel sensitization in the general population is primarily a result of repeated dermal contact/exposure with nickel-releasing consumer products (e.g., jewelry, watches, eyeglasses, etc.) over prolonged periods of time (NiPERA, 2016; Haber et al., 2017).

The prevalence of nickel sensitivity in the North American population is significant, with a higher percentage of women than men being sensitized to nickel due to women's exposure to nickel-releasing jewelry for cultural and societal reasons. A study of 9,334 subjects found the prevalence of nickel sensitivity among North American women and men to be 23 and 7%, respectively (Warshaw et al. 2014, Haber et al 2017).

How has Nickel Contact Dermatitis been Evaluated Previously?

Original CBRA

As part of the sensitivity analysis (Section 8.5) of the CBRA (JWEL, 2007), the concentration of Ni in soil that might elicit an allergic dermal reaction (nickel contact dermatitis) in nickel-sensitized individuals who come into dermal contact with soil containing Ni was discussed in a semi-quantitative fashion. The CBRA compared an estimated maximum nickel skin loading rate (of 0.7 µg/cm^2), which was approximated using a maximum soil Ni concentration (of 33,000 mg/kg), a soil adherence factor of 0.1 mg soil/cm^2 skin, and a soil Ni bioaccessibility value of 21% to the range of skin loading rates (<0.1 to 1.0 µg/cm^2) for which nickel dermatitis reactions were observed to be unlikely to occur (Menne, 1994). Since the estimated maximum Ni skin loading rate (of 0.7 µg/cm^2) fell within the range which a dermatitis reaction was observed to be unlikely, the CBRA concluded that *'…a dermatological response to nickel in Port Colborne soils…*[was]*…highly improbable for nickel-sensitized individuals.*' (JWEL, 2007).

2014 Update Report

The 2014 CBRA Update Report (Stantec, 2014) expanded the discussion of the literature concerning nickel contact dermatitis and presented a quantitative approach to evaluate the hazards associated with the elicitation of a dermal contact allergic reaction among nickel sensitized individuals resulting from dermal contact with soil containing elevated Ni (Appendix 3D and 3H of the Update Report).

Stantec adopted the use of a (dermal) elicitation dose, the "ED_{10}" – the dose that can elicit an allergic reaction in 10% of allergic individuals under patch test conditions. An ED_{10} of 0.835 µg Ni/cm^2 had been previously developed by Fischer et al (2011) after analyzing data from 16 dermal patch test studies, 5 of which involved nickel (the remaining 11 studies involved 7 other allergens). It is recognized that 0.835 µg Ni/cm^2 was not specific to nickel but rather was representative of all allergens included in the Fischer et al (2011) analysis. Soil-to-skin adherence factors and a revised dermal absorption factor, defined as the product of the fraction of nickel in sweat available for absorption, based on a limited intestinal phase bioaccessibility dataset (of 10.9%) and the dermal absorption rate of 2.8% were used, in combination with the ED_{10}, to develop a soil screening level that could elicit an allergic dermal reaction in Ni sensitized individuals. Hazard Quotient (HQ) values were developed by comparing the Ni soil concentration of interest (e.g., the Ni soil concentration for specific Port Colborne zones) with the soil screening concentration that could elicit an allergic reaction among sensitized individuals.

The Update Report (Stantec, 2014) generally concluded (in Appendix 3H) that the potential risk associated with nickel contact dermatitis occurring among sensitized individuals (as a result of coming in contact with different soil types) was minimal.

MECP Comments

While MECP (2016) did not have any concerns with the general approach used in the Update Report (Stantec, 2014), several limitations were identified. The MECP (2016) indicated that because of these limitations and *'...the inherent challenges in assessing the direct soil Ni contact dermatitis pathway, risks can only be roughly evaluated at this present time.'* The MECP (2016) presented alternative exposure scenarios (i.e., a typical and an atypical scenario) and associated input parameters (i.e., alternative soil adherence factors and a 10-fold uncertainty factor on Fischer's ED_{10}). The MECP (2016) concluded for the 'typical scenario' that *'…soil Ni concentrations between 4,000 and 40,000 mg/kg encompass the range where there would be a low concern of Ni induced contact dermatitis for the Ni-sensitized subpopulation residing in Port Colborne.'* However, for the 'atypical scenario', MECP concluded that *'...soil Ni concentrations between 800 and 8,000 mg/kg encompass the range where there would be a low concern of Ni induced contact dermatitis for high end estimates.'*

The analysis and comments provided by the MECP (2016) support the view that the allergic contact dermatitis pathway is associated with many areas of uncertainty, that make it challenging to provide a narrow concentration range of Ni in soil that might elicit a dermal reaction among Ni sensitized individuals following dermal contact.

An Allergic Dermal Reaction in Sensitized Individuals from Soil– Oral Exposure

A new approach to assessing allergic contact dermatitis for Ni has been undertaken in the PCCAP.

Since the time of the Update Report (Stantec, 2014), Haber et al (2017) developed an oral toxicity reference value (TRV) designed to limit potential dermal allergic reactions among nickel sensitized (allergic) individuals following ingestion of nickel. Data from three studies (all of which confirmed nickel sensitivity among participants using skin patch tests) that administered a single dose of nickel sulphate (or placebo) under fasting conditions were used to arrive at a point of departure (POD) for the development of a TRV. Based on the Haber et al analysis, a POD of 0.30 mg Ni (or 4.3 µg/kg/d based on an assumed 70 kg body weight and rounded to 4.0 µg/kg/d) was developed for systemic contact dermatitis in nickel sensitized individuals.

Haber followed the International Programme on Chemical Safety guidance for immunotoxicity risk assessment guidelines (ICPS, 2012) as it relates to application of uncertainty factors. Specifically, Haber indicated that while an intraspecies uncertainty factor (to account for variability in the human population) is appropriate for the initiation of sensitization, an elicitation response (the endpoint of focus here) is already based on effects observed among susceptible individuals. As such, an intraspecies uncertainty factor of 1 was applied to the POD, resulting in a TRV of 4.0 µg/kg/d. Haber et al indicated that the TRV is in addition to dietary Ni exposures as none of the studies used to develop the POD controlled for Ni exposure from diet.

The Update Report spoke to the prevalence of nickel sensitization among children (Stantec, 2014). The findings from Bruckner et al (2000), as presented in the Update Report, suggest that nickel sensitization can occur in children as young as 6 months of age. Fortina et al (2010), as presented in the Update Report, indicated that of the 321 children under the age of 3 years of age that underwent a patch test, 28.6% tested positive to nickel sulphate. Based on these facts, the receptor chosen for this assessment was a sensitized young child ('toddler').

The exposure scenario used here to evaluate the potential for an allergic dermal reaction in Ni sensitized (allergic) individuals from ingesting local soil and garden produce containing Ni considered the following:

- the characteristics (e.g., soil ingestion rate, body weight, etc.) of a toddler (age 6 months to 4.5 years) under a reasonable maximum exposure (RME) scenario;

- the inclusion of six (6) exposure pathways, including: incidental soil ingestion, indoor dust ingestion, the ingestion of particles following inhalation, consumption of home garden produce, fruit and local eggs;

- Ni exposure from the consumption of supermarket foods was not considered, as the Haber TRV is to be applied to exposures that are in addition to dietary sources. However, dietary Ni from local foods was considered, as Ni levels in local garden produce appeared to be elevated relative to levels reported for similar products by the Health Canada Total Diet Survey (Health Canada, 2020).

Here, risk-based soil concentrations (RBSCs) have been developed to be protective of an allergic dermal reaction (following oral exposures) among Ni sensitized children in Port Colborne. The exposure scenario outlined above and the Haber et al TRV (4.0 µg/kg/d) were used in an iterative process whereby Ni soil concentrations were increased until exposures were equal to the Haber et al TRV of 4.0 µg/kg/d, producing a hazard quotient (HQ) value of 1.0. Ni soil concentrations below the RBSC are not expected to result in an allergic dermal contact reaction (from oral exposures) among Ni sensitized (allergic) children.

The difference in RBSC among the different soil types is a result of the relative bioavailability determined for each soil type. The RBSCs were set at a HQ value 1.0, and the equation was then solved to determine the associated exposure required to obtain the HQ of 1.0 (Table 1).

$$HQ = \frac{\text{EXP}}{TRV}$$

Where:

HQ	=	hazard quotient – sensitized (allergic) toddler at the RBSC (1.0 unitless)
EXP	=	oral Ni exposure of a Ni sensitized toddler at the RBSC (0.004 mg/kg/d)
TRV	=	Haber et al toxicity reference value (of 0.004 mg/kg/d)

Table 1 – Oral Exposure Estimates (mg/kg/d) of Ni Sensitized Toddler at the RBSC[1]

Exposure Pathway	Exposure Estimates at different RBSC (mg/kg/d)		
	Organic soil (**550 *mg/kg***)	Fill (**900 *mg/kg***)	Clay (**1,200 *mg/kg***)
Incidental ingestion of soil	0.00072	0.00077	0.00074
incidental ingestion of indoor dust	0.00064	0.00069	0.00066
ingestion of inhaled dust particles	0.000005	0.000005	0.000005
Ingestion of backyard produce	0.0017	0.0017	0.0017
ingestion of backyard fruit	0.00095	0.00095	0.00095
ingestion of local eggs	0.000006	0.000006	0.000006
Total Exposure	***0.004***	***0.004***	***0.004***

[1]RBSC were calculated at a HQ value of 1.0 for each soil type

An Allergic Dermal Reaction in Sensitized Individuals from Soil– Dermal Exposure

The Update Report (Stantec, 2014a) and the MECP (as part of its review comments) evaluated the concentration of Ni in soil that could elicit a reaction (under patch test conditions) among children already sensitized to Ni.

Dermal Elicitation Dose

The elicitation dose (μg Ni/cm^2 skin), the dose that can elicit an allergic reaction in 10% of allergic individuals under test patch conditions (ED_{10}) developed by Fischer et al (2011), was used by Stantec (and again by the MECP) to evaluate risks associated with a dermal allergic reaction occurring in Ni sensitized children. Fischer et al developed the median ED_{10} of 0.835 μg/cm^2 by identifying and reviewing data from 16 individual dermal patch test studies, 5 of which involved nickel. The remaining 11 studies involved 7 other allergens. In other words, 0.835 ug/cm^2 is not specific to nickel[1].

Citing 'standard risk assessment practices, the MECP (2016) applied an uncertainty factor of 10 (for use of a LOAEL and to account for intra-individual variability) to the Fischer et al (2011) ED_{10} of 0.835 μg/cm^2, resulting in an elicitation dose of 0.0835 μg/cm^2. Given the uncertainty of extrapolating the results of Fisher et al to the general population, the MECP (2016) indicated

[1] Fisher et al (2011) provided median ED_{10} in μg/cm^2 (with 95% confidence intervals) from 5 nickel-specific studies. One of the five (5) studies was identified by Fischer et al as an outlier and was excluded from further consideration. Of the four (4) remaining nickel-specific patch test studies, the mean ED_{10} is 0.985 μg/cm^2. The reported upper and lower 95% confidence limits of ED_{10} values spanned 4.04 and 0.066 μg/cm^2, respectively.

that a range of elicitation doses should be applied (0.0835 μg/$cm^2$to 0.835 μg/cm^2). As highlighted by Haber et al., International Programme on Chemical Safety guidance for immunotoxicity risk assessment guidelines (ICPS, 2012) indicates that while an intraspecies uncertainty factor (to account for variability in the human population) is appropriate for the initiation of sensitization, an elicitation response is already based on effects observed among susceptible individuals. The elicitation ED_{10} of 0.835 μg/cm^2 dose was derived from sensitized populations and does not represent a NOAEL but rather a median value from 16 different studies. In contrast, the sensitizing concentration for nickel was reported to be 140 μg Ni/cm^2 – approximately 140 times greater than the reported elicitation dose (ED_{10}) (Fischer et al., 2011).

Soil Adherence Values

A soil adherence factor (AF) is required for the assessment of exposure via the dermal exposure pathway. The AF is an estimate of how much soil would stick to the skin, thereby providing a pathway for exposure via the skin. An AF of 1 mg/cm^2 was used by the MECP (2016) to facilitate an 'atypical' (or high-end contact) exposure scenario. The MECP (2016) cited Part E (Supplemental Guidance for Dermal Risk Assessment) of the US EPA Risk Assessment Guidance Document (US EPA, 2004) and indicated that the selected value (of 1 mg/cm^2) falls between the 95th percentile AF for children playing in dry soil (0.4 mg/cm^2) and the 95th percentile AF for children playing in wet soil (3.3 mg/cm^2)[2].

A more recent US EPA Child-Specific Exposure Factors Handbook (US EPA, 2008) provides recommended activity- and body-part specific AF values (Table 7-4 of US EPA, 2008). Except for two activities ('playing in mud' and 'playing in sediment'), none of the recommended AF values for the face, hands, arms, legs, and feet exceeded 0.2 mg/cm^2. The highest recommended AF for soil (of 0.20 mg/cm^2 for feet) and was developed using a weighted average of geometric mean soil loadings for gardeners and archeologists working in soil. The study used to derive AF values for 'sediment' indicate that AF values are specific to sediments and intended to for used in exposure scenarios involving children in contact with sediment in coastal shoreline or tidal flats, for example.

Playing in sediment and/or mud may occur on occasion; however, this type of activity is not applicable to typical, repeated contact with soil – the AF values recommended for use by the US EPA (2008) for sediment and mud are specific to these two media and should not be used evaluate contact with soil. Under a typical residential setting in the Port Colborne, repetitive dermal contact with outdoor soil and indoor dust is overwhelmingly the most likely scenario. Using the methods recommended by the US EPA (2008), an area-weighted, activity-specific AF, a value of 0.1 mg/cm^2 was derived here using recommended body-part-specific surface areas for children 6 to < 11 years of age and body-part-specific AF values for high contact 'soil related activities'. The application of this AF value was considered a reasonably conservative approach considering the majority an individual's time will be spent indoors subjected to indoor dust AF values which are approximately 10-fold lower than those associated with soil.

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[2] The older RAGS guidance presents these percentile values, bur the newer child-specific exposure factors handbook reports mean values and indicates that sample sizes are not large enough to consider other indicators of probability distributions, such as percentiles.

As such, the range of Ni soil concentration that could elicit an allergic reaction among Ni sensitized individuals (under patch test conditions) was calculated using the following equation:

$$[Soil] = \frac{\mathrm{ED}}{AF\ x\ DB}$$

Where:

[Soil] = Ni soil concentration that could elicit a dermal reaction in 10% of a sensitized (allergic) population (µg/g)

ED = elicitation dose (µg Ni/cm^2 skin), the dose that can elicit an allergic reaction in 10% of allergic individuals under patch test conditions (ED_{10}). Mean of the four Ni specific studies 0.985 µg/cm^2. 95% Confidence interval span 0.066 µg/cm^2 – 4.04 µg/cm^2.

AF = soil adherence factor – a range of 0.0001 g/cm^2 (or 0.1mg/cm^2) based on the recommended methods of the US EPA (2008).

DB = dermal bioaccessibility approximation (10.9%) based on intestinal phase bioaccessibility data from the CBRA.

Table 2 – Ni Soil Concentrations (mg/kg) that may Elicit a Dermal Reaction Among Ni Sensitized Individuals Following Dermal Contact with Soil

Soil Nickel Concentration[1]	Soil Contact Exposure Scenario		
	Lower Confidence Limit of ED_{10}	Mean Nickel ED_{10}	Upper Confidence Limit of ED_{10}
	6,000	90,000	371,000

[1]Soil concentrations have been rounded.

The confidence intervals surrounding the reported Ni ED_{10} values range from 0.066 to 4.04 µg/cm^2, an approximately 61-fold range of values. This large range (uncertainty) contributes to the inability to provide a more definitive Ni soil concentration range that could result in a dermal reaction among Ni sensitized individuals.

Table 3 – Ni Soil Concentrations (mg/kg) that may Elicit a Dermal Reaction Among Ni Sensitized Individuals Following Oral Exposure and Dermal Contact with Soil

Route of Exposure	Risk-Based Soil Concentrations (mg/kg)		
	Organic Soil	Fill	Clay
Oral RBSC	500	900	1,200
Dermal RBSC	6,000 – 371,000	6,000 – 371,000	6,000 – 371,000

A comparison between Ni soil concentrations that may elicit a dermal reaction among some Ni sensitized individuals following oral exposure (Table 1) and concentrations that may result in a dermal reaction following dermal contact (Table 2) suggest that the oral route of exposure may be more sensitive compared to dermal contact for elicitation of dermal reactions (Table 3).

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