

Systemic contact dermatitis after oral exposure to nickel: a review with a modified meta-analysis

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Systemic contact dermatitis can be elicited experimentally in nickel-sensitive individuals by oral nickel exposure. A crucial point interpreting such experiments has been the relevance of nickel exposure from drinking water and diet. The aim of this meta-analysis study on former nickel-exposure investigations was to provide the best possible estimation of threshold values of nickel doses that may cause systemic contact dermatitis in nickel-sensitive patients. 17 relevant investigations were identified, and statistical analyses were performed in a stepwise procedure. 9 studies were included in the final dose–response analysis, which divided the studies into a homogenous middle group of 5 studies and 2 groups of 2 studies with a higher and lower response frequency, respectively, described by logistic dose–response curves shifted in parallel. On the basis of these curves, calculations were made of the doses that, theoretically, would cause systemic contact dermatitis in exposed nickel-sensitive patients. The results from the 2 most sensitive groups show that 1% of these individuals may react with systemic contact dermatitis at normal daily nickel exposure from drinking water and diet, i.e. 0.22–0.35 mg nickel.

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Systemic contact dermatitis is seen as flare-up of previous dermatitis or *de novo* dermatitis similar to allergic contact dermatitis. While systemic contact dermatitis from medicaments is a well-established entity, systemic reactions to metals, particularly to nickel, has been regarded as controversial (1, 2). 1 reason for this is that reactions to a ubiquitous hapten, such as nickel, are not easily identified with certainty because it is difficult to measure and control daily exposure through drinking water and diet.

However, there is significant evidence that oral intake of nickel can induce systemic contact dermatitis in nickel-sensitive individuals. Flare-up reactions of previous nickel patch test sites after systemic oral exposure appear to be hapten specific (3). There appears to be a dose–response relationship, and the overall trend from several oral exposure studies is that the severity of the reaction after exposure and the number of reacting nickel-sensitive individuals increase with higher exposure doses (Table 1) (4–20). Until now, nobody has tried to summarize the data from the oral exposure studies to determine an oral nickel exposure threshold for elicitation of

systemic contact dermatitis. A complicating factor, making it difficult to draw definite conclusions, is the great variation in the protocols of the different studies and in the degree and extension of the individual's clinical reactions.

Whether or not the nickel exposure from drinking water and the diet can induce systemic reactions is still controversial, as unphysiologically high nickel doses were used in most of the conducted studies. The doses used in the studies vary from 0.3 mg to 5.6 mg nickel (Table 1), while normal daily dietary nickel intake has been found to vary from 0.02 mg to 0.48 mg nickel (21–32). However, some studies have shown that an exposure dose equivalent to the maximal nickel exposure through the diet (0.9 mg nickel per day) (21) can induce systemic reactions in some nickel-sensitive individuals (6, 8, 9, 13, 20). Additionally, dietary intervention studies (5, 33–36) indicate that exposure to nickel in diet and drinking water could be a contributing factor to systemic contact dermatitis.

The aim of the conducted study was to determine the best possible threshold values for oral nickel exposure which would elicit allergic

Table 1. Characteristics of the different studies

Criteria's of inclusion	Study design	Group size	Dose (mg Ni)	Type of exposure and conditions	Definition of positive reactions	Time before evaluation	References
PPT, HNA and HE	DB, SE	1 × 12	0, 5.6	NiSO ₄ in capsule, not fasting	FUE, WHE and EB	6 + 30 hr	Christensen and Möller (4)
PPT and HE	DB, SE	1 × 28	0, 2.5	NiSO ₄ in capsule, not fasting	FUE and/or WHE	2–72 hr	Kaaber et al. (5)
PPT, HNA and HE	DB, SE	1 × 11	0, 0.6, 1.2, 2.5	NiSO ₄ in capsule, not fasting	FUE, WHE and EB	48–72 hr	Kaaber et al. (6)
NPT* and HNA	NB, SE	1 × 4, 1 × 7	4.0	NiSO ₄ in capsule, not fasting	FUE, WHE and EB	72 hr	Veien and Kaaber (7)
PPT and HE	DB, DE	1 × 10	0, 0.5	NiSO ₄ in capsule, not fasting	WHE	0–48 hr	Jordan and King (8)
PPT and HE	NB, SE	3 × 5	0.6, 1.25, 2.5	NiSO ₄ in capsule, over night fasting and 1 hr after	FUL, WHE and EB	0–72 hr	Cronin et al. (9)
PPT and HE	DB, DE	1 × 22	0, 2.0, 4.0	NiSO ₄ in capsule, not fasting	WHE	24 + 72 hr	Burrows et al. (10)
Not documented	DB, SE	1 × 49	0, 2.24	Not documented	Not documented	Not documented	Bedello et al. (11)
Not documented	DB, SE	1 × 20	0, 2.4	Not documented	Not documented	Not documented	Sertoli et al. (12)
PPT, HNA and HE	DB, SE and DE	1 × 6, 2 × 10	0, 0.4, 2.5, 5.6	NiSO ₄ in capsule, not fasting	FUE and/or FUL and/or EK	72 hr	Gawkrödger et al. (13)
PPT, HNA and/or HE	NB, SE	1 × 10, 1 × 19	0, 2.5	NiSO ₄ in capsule, not fasting	FUE and/or FUPT and/or EB	24 + 48 hr	Roduner et al. (14)
PPT and HNA	DB, SE	1 × 131	0, 2.5	Ni-salt in tablet; not fasting	FUE and/or FUPT and/or EB	0–96 hr	Veien et al. (15)
PPT and HNA	NB, SE	1 × 25	2.24	NiSO ₄ in capsule, not fasting	FUE and/or FUPT and/or EB	0–48 hr	Santucci et al. (16)
PPT and ECZ	DB, SE	1 × 19, 1 × 9	0, 2.5	NiSO ₄ in capsule, not fasting	FUE and FUPT	0–24 hr	Möller et al. (17)
PPT, HNA and HE	NB, SE	2 × 20	0.8†	⁶¹ Ni in water, fasting 12 hr before and 4 hr after	FUE and/or WHE and/or EK	0–72 hr	Nielsen et al. (18)
PPT	DB, SE	2 × 10, 1 × 9	0, 1.0, 4.0	NiSO ₄ in capsule, over night fasting and 1 hr after	FUPT	24 hours	Hindsén et al. (19)
PPT and HE	DB, SE	4 × 10	0, 0.3, 1.0, 4.0	NiSO ₄ in capsule, fasting 12 hr before	FUE and/or FUPT and/or EB	24 hr	Jensen et al. (20)

Inclusion criteria: ECZ = eczema; HE = hand eczema; HNA = history of nickel allergy; NPT = negative patch test; PPT = positive patch test; design DB = double blinded; NB = not blinded; SE = single-exposure; DE = double exposure over 2 days. Definition of positive reaction: FUE = flare-up of former eczema; FUPT = flare-up of former patch test; WHE = worsening of hand eczema; EB = erythema on the body.

*Patients with negative routine patch tests were challenged orally with nickel.

†Average exposure dose. Persons were exposed to 12 µg/kg bodyweight.

contact dermatitis in nickel-sensitive individuals by combining the data from published oral exposure studies in a meta-analysis.

Methods and Statistical Analyses

Relevant studies published from January 1966 to November 2004 were identified by searching MEDLINE, EMBASE and BIOSIS using the words: nickel, oral, challenge, exposure, hypersensitivity, sensitivity, allergy, systemic provocation and contact dermatitis in different combinations. Additionally, the databases were searched by the use of the 'Related Articles' function and by searching the publications by specific authors in the scientific area. Finally, relevant references were localized by the use of the reference lists in review articles. Though probably most of the relevant publications were localized by these methods, this study is not a formal meta-analysis (or series of meta-analyses), which includes all publications on the subject.

Standard statistical methods based on the binomial distribution of the number of positive reactions were used for the calculation of confidence intervals for response frequency and for tests of differences in response between doses within the same study or between 2 studies at the same dose.

Logistic regression analysis was applied to estimate dose–response relations and for comparison of dose–response relations between studies. These methods are based on the assumption that patients are randomly divided into the various dose groups. It should be pointed out that the dose–response modelling analysis does not apply to the experimental situation where the same group of patients is tested with different doses, including a dose of 0 mg nickel (placebo). In this case, it would be a natural assumption that if a patient has shown a positive reaction to a given dose, that person will also show a positive reaction to all higher doses. This may be checked by inspection of the individual responses to the doses in question, but the reported response rates do not contain this information except when none or all patients react.

Paired responses to 2 different doses were compared by McNemar's test, while Fisher's test or Chi-square tests were used for unpaired responses (data not shown). Multiple logistic regression analysis was applied to determine which studies deviate significantly from the mean under the assumption that the slopes of the dose–response curves were similar. However, since it is not correct to include the same patients more than once in this analysis, it was chosen only to use the

response rate closest to 50% from the studies where a single group of patients were tested with more than 1 nickel dose. The analysis was performed according to the backwards elimination procedure as well as the forward selection procedure. In the backwards elimination, the study that deviates the least as well as insignificantly ($P > 0.05$) from the mean of the others is regarded as representing the mean, and in the next step the least non-significantly deviation group among the remaining studies is accepted as representing the mean, etc. This pooling of studies stops when only significantly deviating studies remain. These studies may also be identified by the forward selection procedure, where the study (or the nickel dose–response effect) that deviates most and significantly from the mean is selected first. In the next step, the most significant among those remaining is selected, etc. The selection stops when none of the remaining studies are statistically significant, i.e. $P > 0.05$.

Finally, estimates of ED₅₀ and other lower (threshold) doses were calculated from the logistic dose–response curves by the use of Fieller's method. The statistical analyses were with APL2000[®] software (Maneugistics, Rockville, MD, USA) validated relative to SAS[®] version 8.2 procedures (Proc Freq and Proc Univariate, SAS Institute, Cary, USA, 2001).

Results

From the literature search, 17 studies on oral nickel exposure in nickel-sensitive patients were identified (Table 1). Additional 2 studies were found (37, 38), but these were excluded because the nickel-exposure doses used varied both intra- and interindividually. The aim of the statistical analysis was to conduct a comparative quantitative dose–response analysis including as many of the identified studies, which was proven difficult because of the heterogeneity amongst the identified studies. The 17 studies included 496 individuals and varied in size from 11 to 131 individuals. Different protocols have been used in the various studies, and so the observed differences between the studies may be caused by differences in testing and evaluation methods as well as differences in the tested patient populations.

The distribution of the number of positive reactions with 95% confidence limits plotted against the dose in logarithmic scale showed that the limits in most cases were rather wide due to the relative small number of patients (data not shown). There was a clear tendency to increasing reaction rate with increasing dose, but a more detailed analysis was needed to evaluate

how the dose–response relations might differ between the studies.

Some of the studies had positive responses to placebo [studies 8, 10, part of 13 (the study consisted of both single and double exposure), 15, 17 and 20]. A comparison of these reactions demonstrated differences between single studies and groups of studies both among studies using double exposure and single exposure (data not shown). Since the majority of the studies used single exposure, it was more rational to continue the analyses with these studies. This meant that the data from studies 8, 10 and parts of 13 were not included (Table 1).

A stepwise multiple logistic regression analysis was performed on the relevant data from 401 patients in the 15 studies where single exposure was used. The result showed a statistically significant dose–response effect ($P < 0.0001$), and it was found that the studies 9, 14, 15 and 17 deviated significantly from the remaining 11 studies, which showed an acceptable agreement (Fig. 1). The 4 deviating studies could be divided into 1 group with 3 studies (studies 14, 15 and 17) and 1 separate study (study 9). The group comprising the 11 studies had an intermediary dose–response curve, while the group of 3 had a lower dose–response curve, and the separate study had a higher response rate. The hypothesis of parallel dose–response curves was acceptable. However, the analysis has 2 weaknesses. The data included 2 studies without placebo testing (studies 16 and 18), and it contained 3 studies (studies 15, 17 and 20) which had positive responses to placebo.

It is an open question whether it from a biological and statistical point of view is meaningful to compare the dose–response relations from all the

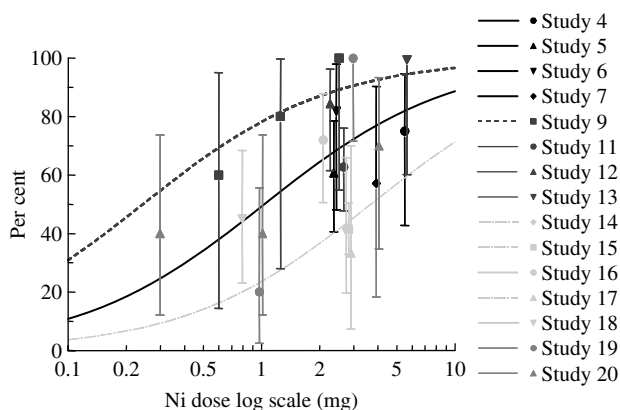


Fig. 1. Observed rates of response with 95% confidence limits and fitted dose–response curves in studies with single exposure. Studies 4, 5, 6, 7, 11, 12, 13, 16, 18, 19 and 20 form a homogenous group with a common dose–response curve (in black), studies 14, 15 and 17 form another homogeneous group (in green) and study 9 forms a third group (in red), which are all significantly different.

single-exposure studies, when the response rates to placebo is positive in some studies, and when some studies have no placebo testing included. Therefore, after exclusion of these 5 studies, an additional analysis was performed on the data from the remaining 9 studies comprising 171 patients. This altered the result of the stepwise multiple logistic regression analysis. In a homogeneous group (studies 5, 6, 7, 11 and 13), an intermediary dose–response curve was found, while 2 groups each comprising 2 studies had a higher (studies 4 and 14) or a lower dose–response curve (studies 12 and 19) (Fig. 2). These 2 groups included only 1 of the deviating studies from the previous analysis.

On the basis of the result from the last analysis, exposure doses corresponding to response rates of 50% (ED_{50}), 25% (ED_{25}), 10% (ED_{10}), 5% (ED_5) and 1% (ED_1) of exposed nickel-sensitive eczema patients were calculated (Table 2). These calculations predict that an oral nickel exposure with 0.22 mg, 0.35 mg or 0.53 mg nickel (depending on which dose–response curve is used) will make 1% of nickel-sensitive patients respond. Similarly, 2% of these patients will react if they are exposed orally to nickel doses of 0.29 mg, 0.45 mg or 0.70 mg, 5% will react to 0.41 mg, 0.65 mg or 1.0 mg nickel, while an exposure to 0.55 mg, 0.87 mg or 1.33 mg nickel will make 10% of the patients react with signs of a systemic contact dermatitis.

Discussion

An extensive literature search identified dose–response data from 17 published studies of oral

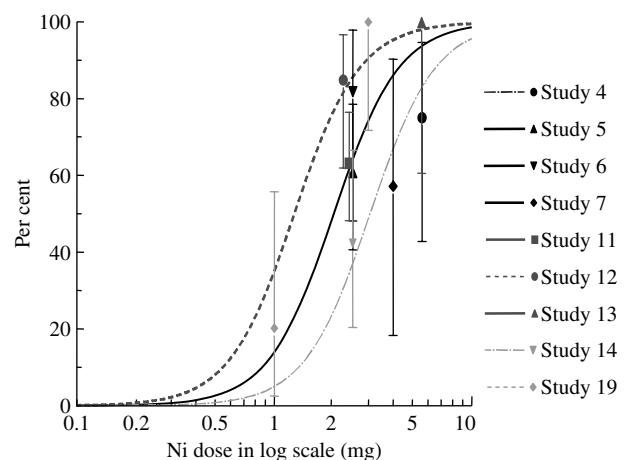


Fig. 2. Observed rates of response with 95% confidence limits and fitted dose–response curves in studies with single exposure and no placebo reactions. Studies 5, 6, 7, 11 and 13 form a homogenous group with a common dose–response curve (in black), studies 4 and 14 form another homogeneous group (in green), and studies 12 and 19 form a third group (in red), which are all significantly different.

Table 2. Estimated doses of ED₅₀ and lower responses with 95% confidence limits

Ni doses (mg)	Studies 12 and 19		Studies 5, 6, 7, 11 and 13		Studies 4 and 14	
	Estimate	95% limits	Estimate	95% limits	Estimate	95% limits
ED ₅₀	1.27	0.77–1.72	2.00	1.47–2.35	3.06	2.15–4.30
ED ₂₅	0.83	0.37–1.19	1.32	0.68–1.69	2.01	1.13–2.74
ED ₁₀	0.55	0.17–0.86	0.87	0.31–1.26	1.33	0.53–1.94
ED ₅	0.41	0.10–0.70	0.65	0.18–1.04	1.00	0.31–1.57
ED ₂	0.29	0.05–0.54	0.45	0.09–0.81	0.70	0.16–1.21
ED ₁	0.22	0.03–0.45	0.35	0.05–0.67	0.53	0.09–1.00

nickel exposure on patients sensitive towards nickel. These studies varied in criteria of inclusion, design of the exposure protocol, numbers of exposure boluses, how the same patients were tested, inclusion of and reactions to placebo, fasting condition prior to exposure, definition of positive reaction to exposure and the time of evaluation after exposure, which made a strict meta-analysis including all studies impossible. Therefore, it was necessary to modify the analysis and exclude data from studies which differed significantly from the majority to be able to determine the best possible threshold values for oral nickel exposure, which would elicit allergic contact dermatitis in nickel-sensitive individuals.

In the overall evaluation of the identified studies, there seem to be a tendency that increasing exposure doses results in increasing reaction rates, but a more detailed analysis was needed to evaluate how the dose–response relations might differ between the studies.

After conducting several analyses and excluding studies with double exposure, studies with responses to placebo and studies without placebo testing, the final model included 9 studies with oral nickel exposure conducted on a total of 171 individuals. The result was a homogeneous group including 5 studies (studies 5, 6, 7, 11 and 13) with an intermediary dose–response curve, while 2 groups each including 2 studies had a higher (studies 4 and 14) or a lower dose–response curve.

On the basis of the result of the last modified meta-analysis, theoretical exposure doses predict that an oral nickel exposure with 0.22 mg, 0.35 mg or 0.53 mg nickel (depending of which dose–response curve is used) will make 1% of nickel-sensitive patients respond. Similarly, 10% of these patients will react if they are exposed orally to nickel doses of 0.55 mg, 0.87 mg or 1.33 mg nickel (Table 2).

It should be emphasized that the tested individuals included in the studies do not represent the majority of the population but are persons allergic to nickel, who have consulted a

dermatologist. In the majority of the cases, the patients had symptoms which could indicate a systemic component in their disease, and many patients had had chronic hand eczema (Table 1) which flared up after the oral exposure. Using the 2 ‘most sensitive’ statistical calculations, the model predicts that 1% of these patients can be expected to get a systemic reaction to the nickel content of a normal diet, e.g. exposures between 0.22 mg and 0.35 mg nickel and that 10% of them would react to exposures between 0.55 mg and 0.89 mg nickel which theoretically could be attained by consuming food with a high level of nickel, by drinking water contaminated with nickel from the pipes or taps and/or by drinking a large volume of water containing a high level of nickel while fasting.

Nickel exposure from drinking water and other beverages is usually considered to be negligible, although exceptions occur. In most studies, the nickel levels in groundwater and drinking water have been in the range of 1–10 µg per litre (39–45). However, some studies have found water samples containing higher levels. Andersen et al. (44) found the nickel levels in most of the tap water samples from the Copenhagen area to be lower than 35 µg per litre, but there were considerable variations in the amount of nickel at different times of day, from tap to tap and in hot versus cold water. A statutory order on water quality and inspection of water supply facilities from 2001, the Danish Ministry of Environment (46) lowered the maximum level of nickel permitted in drinking water from 50 µg per litre to 20 µg per litre. A recent survey (47) found that the nickel concentrations in the water in 2 out of 20 water supply facilities and in 2 out of 37 sources exceeded the demands to the quality of the drinking water. Andersen et al. (44) found that an additional factor which increases the nickel level in drinking water is that the longer the water is allowed to be in the pipes and the taps the more nickel will be dissolved from the metal to the water. They found concentrations of nickel up to 490 µg per

litre in the first 250 ml of drinking water. After having the tap run for 5 min, they found much lower nickel levels, which could indicate that nickel is released from the pipes and taps and concentrated in still water.

If only the maximum level of nickel permitted in drinking water in Denmark at the moment is obtained (20 µg per litre), a person can consume up to 40–60 µg nickel per day through the drinking water. According to the findings in the final model, this will be the equivalent of 1/4 of the dosage of nickel which will make 1% of the most sensitive nickel-allergic patients seen by dermatologists react with a systemic contact dermatitis response. If a relatively large part of the daily water intake is consumed on an empty stomach, e.g. if a person starts the day with a cup of coffee or tea before eating breakfast, the uptake and contribution of nickel from the drinking water will probably be of relatively more importance and therefore contribute more than 1/4 of the dosage that can result in a systemic response.

The different outcomes of the studies may reflect variations in study design and in differences in the patch tested nickel-sensitive individuals. Different protocols have been used in the various studies, and some of the studies were not conducted in a double-blind manner. In many of the studies, only a very small number of subjects have been tested. The criteria for the selection of test persons have not been standardized. In some studies, a positive patch test to nickel was the only inclusion criterion; 1 study (study 7) was performed on subjects with hand eczema but with a negative patch test, in others the subjects had a positive patch test and hand eczema and/or a history of nickel dermatitis. Neither have the criteria been standardized for identifying a positive reaction to the oral challenge. The time between challenge and evaluation is not the same in the various studies, varying from 0 hr to 72 hr or more. In studies with the shortest time frames, this could have led to an underestimation of the number of subjects reacting to the oral challenge. It has not always been specified whether the subjects had fasted overnight or whether there were other dietary restrictions. In some studies, a single bolus challenge was used, while in others they used a double bolus challenge. The absorption and biokinetics following the bolus exposure employed in most oral challenge studies may be quite different from naturally occurring, dietary exposure, where nickel is absorbed incrementally throughout the day. The natural dietary intake of nickel is difficult to estimate, and in most of the oral challenge studies, it was not taken into account. Total dietary

nickel intake and absorption can be highly variable and difficult to estimate precisely. This depends both on the composition of the diet and on such factors as how the food had been prepared, whether it was fresh or canned food and/or whether it was contaminated during processing or by kitchen utensils. There may also be regional differences in the nickel content of various foods. In most cases, there is probably only a small amount of nickel in drinking water, but as shown in some studies, drinking water may be contaminated with nickel. A particular problem in the performed modified meta-analysis is that no distinction was made between the different end points (definition of positive reaction to exposure) in the various studies. I used end point in some studies, flare-up of a recurrent vesicular hand eczema, which is the most common clinical manifestation of systemic nickel contact dermatitis, is a very complex disease and may be precipitated by a number of stimulants.

It has not been attempted to extend the logistic dose-response analysis to include variables describing differences between the studies such as those just mentioned. From a statistical point of view, the main problem is undoubtedly the variation in background responses between the studies and in particular how to incorporate this heterogeneity into a general dose-response analysis. Therefore, the decision was made to exclude studies with positive responses to placebo and studies without placebo testing, which meant that some reliable studies may not have been used in the final analysis (studies 15, 16, 17, 18 and 20). However, adjusting for a placebo effect would probably shift a theoretical dose-response curve in parallel to the right, resulting in higher threshold values and thus making it impossible to note responses to the lower exposure doses.

It is believed that the analyses performed represent a reasonable and at the moment best possible systematic approach given the limited and rather heterogeneous data.

In conclusion, oral exposure to nickel may lead to systemic contact dermatitis in a dose-dependent fashion. The amount of nickel in food and drinking water will under normal circumstances only provoke a systemic reaction in a minority of the nickel-allergic patients seen by dermatologists.

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