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Nickel (soluble nickel compounds, e. g. nickel acetate, nickel chloride and nickel sulfate) – Addendum: re-evaluation of EKA

Assessment Values in Biological Material – Translation of the German version from 2021

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area has re-evaluated the correlation between inhalational exposure to soluble nickel compounds (e.g. nickel acetate [373-02-4], nickel chloride [7718-54-9] and nickel sulfate [7786-81-4]) and urinary nickel excretion (exposure equivalents for carcinogenic substances (EKA)). The review of the available literature identified several studies that provided regression equations on this relation. However, the values for urinary nickel excretion predicted from these studies varied considerably. Since EKA cannot be determined with sufficient reliability, they are withdrawn.

EKA (2020)	**not established**
BAR (2009)	**3 µg nickel/l urine** Sampling time: for long-term exposures: at the end of the shift after several previous shifts
MAK value	–
Carcinogenicity (2001)	Category 1
Sensitization (1973, 2001)	Sah

Re-evaluation

For soluble nickel compounds, exposure equivalents for carcinogenic substances (EKA) were evaluated in 2004 (translated in Angerer 2010). This was related to exposure concentrations of 25, 50 and 100 µg Nickel (Ni)/m^3. In 2017, the Committee on Hazardous Substances (AGS) published an exposure-risk relationship (ERB) for nickel compounds (AGS 2017), in which tolerance and acceptance values for the respirable (R) fraction of nickel dusts were defined. The acceptance value is 6 µg Ni/m^3. The occupational exposure limit (Arbeitsplatzgrenzwert; AGW) analogue value (for the endpoint pneumonia) was set at 6 µg Ni/m^3 for the R fraction. A value for the inhalable fraction was not established due to a lack of reliable conversion data.

The biological reference value (BAR) is 3 µg Ni/l urine (translated in Schaller 2016). Against this background, the existing EKA were checked for whether it could be extrapolated into this low exposure range. For this purpose, a literature search was conducted to identify new publications that also cover exposures in the low-concentration range.

The EKA valid so far were based on studies with regression equations on the relationship between nickel concentrations in the workplace air and urinary nickel excretion (Nieboer et al. 1999; Oliveira et al. 2000; Tola et al. 1979). Another study (Bernacki et al. 1980) was not included in the evaluation because the values reported differed considerably from those of the other three studies without any plausible explanation.

In the course of the current search, further studies were identified (Ghezzi et al. 1989; Kiilunen et al. 1997 a, b; Werner et al. 1999) in which regression equations were given for the relationship between nickel concentrations in the workplace air and urinary nickel excretion. A brief characterisation of all available studies is provided in Table 1, a presentation of the regression lines in the respective determined concentration range in Figure 1.

The following studies are not suitable for deriving EKA: In the study by Beattie et al. (2017), personal air samplings (filter type GLA 5000) were carried out only in case of conspicuous biomonitoring findings; respiratory protection was used in some cases. Dermal contamination was investigated by hand washing samples and a moderate positive correlation between nickel in urine and hand contamination for all directly exposed nickel workers was observed (correlation coefficient 0.45; $p < 0.0001$). The dermal absorption contributed significantly to the systemic exposure. The authors reported a moderate positive correlation between airborne nickel exposure and urinary excretion (correlation coefficient 0.56; $p < 0.01$), but for "soluble nickel", however, this was only 0.08. A regression equation is not given in the publication. The review paper by Nieboer et al. (1999) is not considered because only the regression equation is reported but no individual data. Kiilunen et al. (1997 a) conducted stationary air measurements in an electrolytic nickel refinery (> 95% nickel sulfate) for six to eight hours during one shift with a 37-mm sampler and personal air samplings with a 25-mm sampler. In case of respiratory protection, measurements were taken under the mask. Nickel concentrations in urine were determined. Additional blood tests at the beginning of the study (mean value (MV): 6–26 nmol Ni/l; maximum: 28 nmol Ni/l) and at the end of the fourth day (MV: 18–59 nmol Ni/l, maximum: 77 nmol Ni/l) were performed. There was no correlation between nickel concentrations in blood or urine and the air at the workplace. In another study in the electroplating shop (Kiilunen et al. 1997 b), stationary air measurements were also made over one shift with a 37-mm sampler and personal air samplings with a 25-mm sampler. While wearing respiratory protection, air measurements were conducted under the mask, with about one-third of the workers wearing respiratory protection.

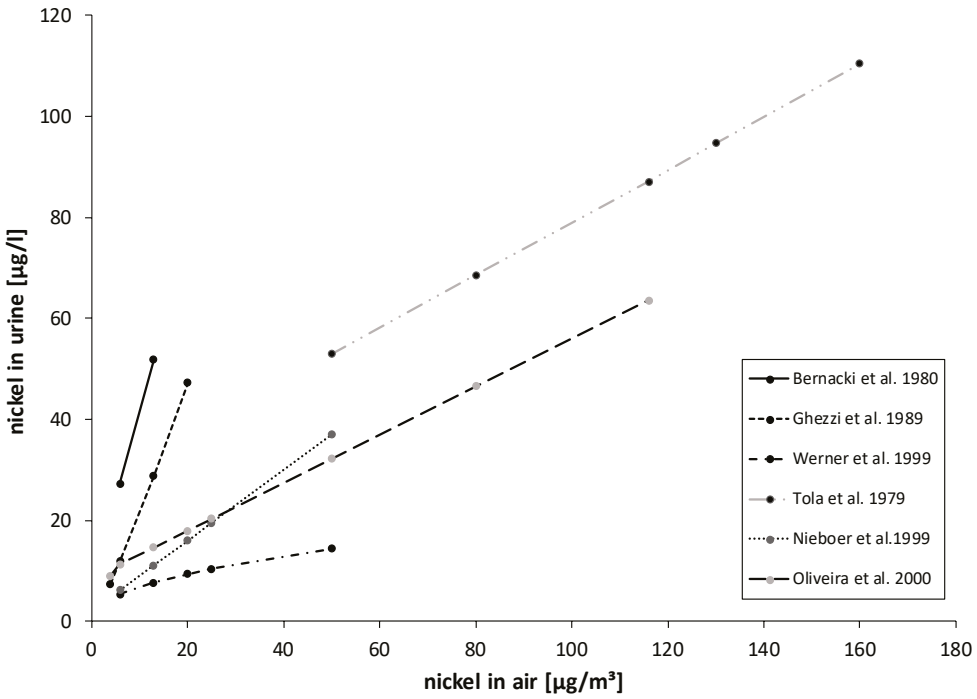

Fig. 1 Correlations between nickel in air and in urine in the respective concentration range measured in the studies for soluble nickel compounds

Under the mask, 1.6 µg Ni/m³, outside 11.4 µg Ni/m³ were measured. The persons in both publications by Kiilunen et al. (1997 a, b) often wore respiratory protection during activities with higher exposure. Consequently, the authors observed no correlation between airborne exposure and urinary excretion or very low excretion values at higher airborne exposures.

In the following studies, regression lines were obtained covering a concentration range in the air at the workplace from 1 to 100 µg Ni/m³:

In the study by Bernacki et al. (1980) in the electroplating industry, personal air samplings were made with a 37-mm sampler over (almost) the entire shift. Work was carried out without respiratory protection and air concentrations at the workplace ranged from 0.5 to 21.2 µg Ni/m³. There were no correlations between pre- and mid-shift urine values and air concentration. High mid-shift values especially for the measurements in the middle of the working week lead to the suspicion of contamination of the samples. No accumulation occurred over the week. Even though a correlation between end-shift urine values on Friday with the air concentration was shown, the derived regression equation is based on measurement results from only four individuals and leads to considerably higher nickel concentrations in the urine compared to the equations from the other studies.

The study by Tola et al. (1979) from electroplating was based on exposures to nickel sulfate and nickel chloride that, at 30 to 160 µg Ni/m³ air (personal air samplings (37-mm sampler), no respiratory protection) are clearly above the target range of the present evaluation. There was a good correlation between nickel exposure in air from about 35 µg/m³ and nickel concentrations in pre- and post-shift urine, as well as a slight accumulation effect over the week. However, a statement for concentrations below 30 µg Ni/m³ is not possible. The background value (intercept with y-axis, see also Figure 1) of the given regression equation is conspicuously high at 26.8 µg Ni/l urine. Moreover, it concerns a very small collective of only four exposed persons. Additional investigations of blood samples (pre- and post-shift) showed a good correlation between air and plasma levels.

In the publication by Werner et al. (1999) at nickel refineries, exposures were not only to soluble nickel compounds and respiratory protection was used. Personal air samplings ("inhalable dust" (IOM-sampler) and "total dust" (37-mm sampler)) were performed, if possible, over the whole shift, but for at least four hours. In addition, pre-shift and post-shift urine samples were pooled, which presumably led to the derivation of values that were too low and no exact sampling time can be determined. There was no accumulation over the week. The mean values in the post-shift urine were higher than those in the pre-shift urine.

In the publication by Oliveira et al. (2000), studies were conducted in the electroplating industry where exposures to nickel sulfate were present. No respiratory protection was used. Personal air samplings were made only in the first half of the shift, but the second half of the shift should be comparable. The pre-shift values of the exposed persons were higher than those of the controls, but there was no accumulation over the week. The relatively high nickel concentrations in the urine of the control persons are attributed to the air pollution of the Sao Paulo region. The regression equation was given for 13 pairs of values, although only ten persons were actually exposed in the study. The figure which illustrates the regression equation shows only partial correlates to the individual values listed in the corresponding table.

In the study by Ghezzi et al. (1989), exposures to nickel sulfate and nickel chloride were present in the electroplating. Personal air samplings (37-mm sampler) were made over the entire shift and no respiratory protection was used. Exposures above 10 µg/m^3 showed accumulation over the week. The given correlation between air (mean value from Monday to Wednesday) and post-shift urinary nickel concentrations on Thursday is not plausible (especially below 10 µg Ni/m^3) with respect to the available data.

The inhalable particle fraction was recorded in the personal measurements. However, since the particle size distribution at the workplaces is not uniform, it is difficult to convert the concentrations measured to R dust.

Tab. 1 Studies with correlations between nickel in air and in urine

Collective, exposure	Nickel in air	Sampling time	Nickel in urine	References
282 nickel workers (NW) of whom 191 electroplating workers (EPW) 237 non-nickel workers (NNW)	soluble nickel: 7 companies, 26 workers, median: 0.01 mg/m^3 (< 0.01–0.08) total nickel: 8 companies, 30 workers, median: 0.01 mg/m^3 (< 0.01–0.6)	post-shift on 3 consecutive days after 0, 6 and 12 months	NW: median 8.2 µmol Ni/mol crea; 90th perc. 28.5 µmol Ni/mol crea EPW: median 9.4 µmol Ni/mol crea; 90th perc. 31.6 µmol Ni/mol crea NNW: median 5.2 µmol Ni/mol crea; 90th perc.: 12.4 µmol Ni/mol crea	Beattie et al. 2017
7 ♂ exposed, electroplating, 19 controls	personal air sampling: MV 9.3 ± 4.4 µg Ni/m^3 range 0.5–21.2 µg Ni/m^3	Monday, Wednesday, Friday and Monday after 2-week vacation pre-shift, mid-shift and end-shift	exposed: pre-shift: MV 34 ± 32 µg Ni/l mid-shift: MV 64 ± 63 µg Ni/l end-shift: MV 46 ± 32 µg Ni/l controls: MV 2.7 ± 1.6 µg Ni/l	Bernacki et al. 1980
23 ♂ exposed, electroplating (nickel sulfate and nickel chloride), 97 ♂ controls	personal air sampling: A (n = 13): > 10 µg Ni/m^3 (GM 11.2–18.8) B (n = 10): < 10 µg Ni/m^3 (GM 4.2–6.9)	pre-shift, post-shift on 4 consecutive working days (Monday–Thursday)	exposed (GM ± GSD): A: 7.7 ± 2.4 µg Ni/l to 33.4 ± 1.5 µg Ni/l B: 5.4 ± 1.9 µg Ni/l to 9.2 ± 2.0 µg Ni/l controls: 1.59 µg Ni/l	Ghezzi et al. 1989

Tab. 1 *(continued)*

Collective, exposure	Nickel in air	Sampling time	Nickel in urine	References
34 exposed, electrolytic nickel refinery (> 95% nickel sulfate), controls: 30 refinery office staff, 32 non-exposed from Helsinki area	stationary: 6–8 h during a shift: total nickel: 2.8–678 µg Ni/m³ water-soluble nickel: 1–77 µg Ni/m³ acid-soluble nickel: 0.3–5.6 µg Ni/m³ personal air sampling without mask: 4–140 µg Ni/m³	pre-shift and post-shift on 4 working days and the following day off, long-term observation: after the weekend (n = 25), after the summer vacation (n = 23)	exposed: MV 0.09–1.28 µmol Ni/l, max: 2.07 µmol Ni/l, after the weekend: MV 0.023–2.09 µmol Ni/l (95% < 0.6 µmol Ni/l) after a 2-week vacation: 0.26 µmol Ni/l after a 4-week vacation: 0.11 µmol Ni/l controls: MV 0.026 µmol Ni/l, 95th perc.: 0.06 µmol Ni/l	Kiilunen et al. 1997 a
104 exposed, electroplating	stationary: low: 11.9–17.8 µg Ni/m³, high: up to 78.3 µg Ni/m³ personal air sampling without mask: low: 0.5–0.7 µg Ni/m³, high: 5.6–78.3 µg Ni/m³	pre-shift and post-shift on 1–4 days in case of high values, additional sample after the vacation (n = 9)	total (n = 145): 0.16 µmol Ni/l (0.001–4.99), ♀ (n = 63): 0.14 µmol Ni/l (0.005–2.84) ♂ (n = 82): 0.18 µmol Ni/l (0.001–4.99)	Kiilunen et al. 1997 b
10 exposed, electroplating (nickel sulfate), 10 controls (from Zn electroplating)	personal air sampling: GM 2.8–116.7 µg Ni/m³	pre-shift and post-shift on 5 consecutive working days (for controls on 3 days)	exposed: pre-shift: 8.7 ± 7.8 µg Ni/g crea (10.5 ± 7,5 µg Ni/l) post-shift: 14.7 ± 13.5 µg Ni/g crea (20.6 ± 18,1 µg Ni/l) controls: MV 3.7 ± 2.5 µg Ni/g crea (0.3–7.8 µg Ni/g crea)	Oliveira et al. 2000
3 ♂, 1 ♀ exposed, electroplating (nickel sulfate and nickel chloride), 1 ♂ control (low exposed)	personal air sampling: 30–160 µg Ni/m³, mainly nickel sulfate	pre-shift and post-shift during 1 week after vacation as baseline	exposed: pre-shift: ~ 10–60 µg Ni/l[a)] post-shift: ~ 20–120 µg Ni/l [a)] after vacation: MV 6.6 µg Ni/l (3–10 µg Ni/l) control (low exposed): ~ 10 µg Ni/l[a)]	Tola et al. 1979
20 exposed, nickel refinery (not only soluble nickel compounds)	inhalable dust, IOM sampler: 11.4–53.1 µg Ni/m³ total dust, 37-mm sampler: 8.1–28.6 µg Ni/m³	pre-shift and post-shift during 1 week	pre-shift and post-shift: MV 11.1 (2.7–51.5) µg Ni/l	Werner et al. 1999

[a)] estimated from the figure
crea: creatine; GM: geometric mean; GSD: geometric standard deviation; max: maximum; MV: mean value; Ni: nickel

Table 2 shows the urinary nickel concentrations calculated for the concentration range from 1 to 100 µg Ni/m³ using the regression equations of the five evaluable studies. Both in the lower concentration range up to 10 µg Ni/m³ and in the higher range up to 100 µg Ni/m³ the urine concentrations vary greatly across the studies. This is probably due not only to methodological differences, but also to the fact that the amount of nickel taken in at identical exposure concentrations in air is also affected by workplace hygiene. For instance, Beattie et al. (2017) observed statistically significant correlations between contamination of hands and surfaces on the one hand and nickel excretion in urine on the other.

Tab. 2 Relationship between external and internal exposure in five evaluable studies at 1–100 µg Nickel/m³

Air	EKA 2004	Bernacki et al. 1980 (0.5–21.2 µg/m³) [a]	Ghezzi et al. 1989 (≤ 20 µg/m³) [a]	Oliveira et al. 2000 (2.8–116.7 µg/m³) [a]	Tola et al. 1979 (30–160 µg/m³) [a]	Werner et al. 1999 (10–71 µg/m³) [a]
[µg/m³]		y [µg/l] = 6.3 + 3.5 × x [µg/m³]	ln y [µg/l] = 0.41 + 1.15 × ln x [µg/m³]	y [µg/l] = 6.00 + 0.43 × x [µg/m³]	y [µg/l] = 26.78 + 522.75 × x [mg/m³]	ln y [µg/l] = 4.07 + 0.468 × ln x [mg/m³]
1		**10**	**1.5**	*6*	*27*	*2*
6		**27**	**12**	**9**	*30*	*5*
10		**41**	**21**	**10**	*32*	**7**
25	25	*94*	*61*	**17**	*40*	**10**
30		*111*	*75*	**19**	**42.5**	**11**
50	40	*181*	*135.5*	**27.5**	**53**	**14**
100	70	*356*	*300.5*	**49**	**79**	*20*

[a] Exposure range in which measurements were taken in the respective study
bold: exposure range in the respective study; *italics*: calculated values
x: nickel in air; y: nickel in urine

Re-evaluation of EKA

Due to the great variability of predicted nickel concentrations in urine after exposure to nickel concentrations in the range of 1 to 100 µg Ni/m³ air calculated with the regression equations from the present studies, the derivation of EKA is not possible.

The EKA valid so far for soluble nickel compounds are therefore withdrawn.

Notes

Competing interests

The established rules and measures of the Commission to avoid conflicts of interest (https://www.dfg.de/en/dfg_profile/statutory_bodies/senate/health_hazards/conflicts_interest/index.html) ensure that the content and conclusions of the publication are strictly science-based.

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