Nickel and its Compounds

BAR (2009)	**3 µg nickel/l urine** Sampling time: for long-term exposures: at the end of the shift after several shifts
MAK value	**Not established**
Peak limitation	–
Absorption through the skin	–
Sensitization (1972, 1995, 2001)	Sah*
Carcinogenicity (1972, 2001)	Carcinogen Category 1
Prenatal toxicity	–
Germ cell mutagenicity	–
Molecular formula	Ni
Molecular weight	58.69 g/mol
Melting point	1 453 °C
Boiling point	2 732 °C
Vapour pressure at 20 °C	no data
Density at 25 °C	8.902 g/cm^3
log K_{OW}	no data

* The respiratory sensitization has only been demonstrated adequately in the case of water-soluble nickel compounds.

In 1990, nickel and poorly soluble nickel compounds were evaluated and exposure equivalents for carcinogen substances (EKA) established (see BAT Documentation 1990, translated). In 2004, soluble nickel compounds were evaluated and EKA established (see BAT Documentation 2004, translated). In the present Documentation, the database for the derivation of a "Biologischer Arbeitsstoff-Referenzwert" (BAR) for nickel and its compounds will be evaluated.

The MAK Collection for Occupational Health and Safety **2016**
DOI: 10.1002/3527600418.bb744002vere1716

1 Selection of Indicators

In biomonitoring, nickel can be detected both in whole blood and in urine. Due to the comprehensive analytics, especially in the measurement of background exposure, the determination of nickel in whole blood is of minor importance. New analytical techniques, such as inductively coupled plasma mass spectrometry (ICP-MS), will in the future allow for a reliable nickel determination in blood within the relevant range of values. The consequence of the more difficult analytics in blood is that the database for nickel levels in the blood of occupationally non-exposed persons is very limited.

In accordance with present-day standards, the determination of nickel in spontaneous urine samples is the recommended monitoring parameter. Both the analytical prerequisites and the database confirm the suitability of this parameter in occupational-medical monitoring.

2 Methods

For quantitative determination of nickel in body fluids, graphite furnace atomic absorption spectrometry (GF-AAS) and ICP-MS are used. Only these two techniques provide analytical detection limits suitable for quantification of background exposure. For direct measurement of biological samples, the sensitivity of GF-AAS is not sufficient to cover the required concentration range. Therefore, for urinalysis using GF-AAS, the sample preparation requires enrichment of the nickel by chelate formation and extraction in an organic solvent. Using this method, an analytical detection limit of 0.2 µg nickel/l urine is attained (Angerer et al. 1983).

ICP-MS allows the determination of nickel both in whole blood and urine samples in the range of background exposure. For blood analysis, a quantification limit of 0.05 µg nickel/l blood is obtained after dilution of the blood sample and using an internal standard (Heitland and Köster 2006 a). Also for urinalysis, an excellent quantification limit of 0.032 µg/l is obtained after dilution of the urine sample and addition of an internal standard (Heitland and Köster 2004, 2006 b). As a result, the analytical requirements are fulfilled to determine nickel reliably in the background exposure range, both in whole blood and in urine. The possibility of internal and external quality assurance exists for both parameters (Schaller et al. 2002).

As generally in the field of ultra-trace analysis of metals in body fluids, care is to be taken that the sample material is not contaminated during preparation and transport. Sampling equipment and transport containers verified as being safe against contamination of the samples must be used. Samples taken with the proper equipment such as EDTA monovettes® or vacutainers® as well as plastic urine beakers meet these requirements.

3 Background Exposure

3.1 Nickel in urine

In western industrial countries, particularly in Germany, the nickel concentrations in the urine of the general population are found to be relatively uniform. This can be seen from Table 1 in the report of the Federal Enviroment Agency (Umweltbundesamt) (UBA 2001) presenting the results of international studies since 1980. Since its publication, some recent and current studies, particularly from Germany, have appeared.

In 163 female patients of a clinic and polyclinic for dermatology aged 18–46 years, the creatinine-related nickel concentrations are in the range of 0.12–10.43 µg/g creatinine (median 1.22 µg/g creatinine). Per liter urine, the 95th percentiles of nickel excretion in female test persons aged between 18 and 30 years and between 31 and 46 years were 3.77 µg/l and 3.98 µg/l, respectively (Schwegler et al. 2007). As analytical method, GF-AAS after chelate formation was used.

Using a highly sensitive ICP-MS method, Heitland and Köster (2006 b) determined the nickel concentrations in urine samples of 87 occupationally non-exposed adults from northern Germany. The results varied within the range of < 0.032 to 7.2 µg/l. The mean value was 0.76 µg/l, as 95th percentile a value of 2.5 µg/l was calculated. In future, ICP-MS will be the method of choice for the determination of nickel in biological materials.

In a French study involving 100 urine samples from healthy test persons, measurements using ICP-MS revealed median urine excretions of 1.8 µg/l. The reference range given as 5th and 95th percentile was 0.59–4.06 µg/l urine. These results are slightly higher than in the German studies (Goullé et al. 2005).

3.2 Nickel in blood

The blood samples of 130 occupationally non-exposed persons from northern Germany were investigated (Heitland and Köster 2006 a). The age range varied between 18 and 70 years. The concentrations in the blood samples varied from < 0.025–0.8 µg nickel/l, the mean value was 0.11 µg/l. The 95th percentile was calculated to be 0.22 µg/l. No comparable current analytical values are available for the general population.

Complementary to these results, a French study is also available (Goullé et al. 2005). Using ICP-MS, 100 whole blood samples from healthy test persons were analyzed. The median was 2.1 µg/l, the range, given as 5th–95th percentile, varied from 0.09 to 4.18 µg/l. The quantification limit was 0.21 µg/l. These results are higher than the values obtained by Heitland and Köster (2006 a) using ICP-MS.

Table 1 Nickel in urine – Survey of reference data from Germany (UBA 2001)

Author	Test persons	n	Ni in urine [µg/l)]	Method
Mundt-Becker and Angerer (1981)	healthy persons, occupationally not exposed to nickel	39	median: 0.90 95th percentile: 2.0 range: 0.34–2.25	GF-AAS
Heinrich and Angerer (1986)	healthy persons, occupationally not exposed to nickel	106	median: 0.60 95th percentile: 1.70 range: < 0.2–3.9	GF-AAS
Angerer and Lehnert (1990)	healthy persons, occupationally not exposed to nickel	123	median: 0.60 95th percentile: 2.2 range: <0.1–13.3	GF-AAS
Wrbitzky et al. (1995)	administration of a hazardous waste incinerator	22	mean ± SD: 1.00 ± 0.68 median: 1.00 95th percentile: 2.00 range: 0.1–2.0	GF-AAS
Heitland and Köster (2004)	adults, EU residents	63	mean: 0.65 95th percentile: 1.5 range: < 0.035–3.5	ICP-MS
Heitland and Köster (2006 b)	adults, northern Germany	87	mean: 0.76 95th percentile: 2.5 range: 0.035–7.2	ICP-MS
Schwegler et al. (2007)	adults, female patients at a dermatological clinic	163	median: 1.22 µg/g creatinine 95th percentile: 3.9 µg/l range: 0.12–10.4 µg/g creatinine	GF-AAS

Abbreviations: ICP-MS = inductively coupled plasma-mass spectrometry; GF-AAS = graphite furnace atomic absorption spectrometry; SD = standard deviation

4 Evaluation

For the reasons given in Section 3, the evaluation of a BAR is made for nickel concentrations in urine only. In the report of the HBM Commission of the Federal Environment Agency (Umweltbundesamt) national and international studies are cited in which the nickel excretions in urine samples of occupationally non-exposed persons are described (UBA 2001). In the meantime, current national studies based on reliable analytics have been published. As there is no significant difference between the studies from western industrial countries and those carried out in Germany, the data from German studies only will be used to evaluate a reference value for nickel excretion in urine. The most important data from these studies are given in Table 1. The data necessary to evaluate a BAR with regard to median, range and 95th percentile are listed for seven studies available since 1981. The medians or mean values vary from 0.6 to 1.2 µg/l, the 95th percentiles from 1.5 to 3.9 µg/l. The fact that in the study by Schwegler et al. (2007) patients of a dermatological clinic, and in this case women only, were examined must be taken into account. The calculated 95th percentile of 3.9 µg/l is higher than in the other six studies in which the values ranged between 1.5 and 2.5 µg/l.

On the basis of the 95th percentiles given in six German studies, a BAR of

3 µg nickel/l urine

is obtained for the adult German general population.

For long-term exposures, sampling should be carried out at the end of the shift after several shifts.

Evaluation of the BAR on the basis of current German studies is necessary, as nickel excretion is influenced by the nickel content in foods and drinking water. In addition, reliable analytical methods were used in the studies cited, and analysis took place under strict quality assurance conditions.

The evaluated BAR agrees with the reference value for nickel in urine in the publication by the Human Biomonitoring Commission of the Federal Environment Agency (Umweltbundesamt) (2001) (Wilhelm et al. 2004). The BAR established is further supported by the evaluation of reference values contained in the TRACY Protocol (Herber 1999). Here, on the basis of four representative studies, excretion values of 0.9–3.2 µg nickel/l are given for the general population.

5 Interpretation

The determination of nickel in urine is an ultra-trace analysis. For this reason highest demands are to be met with regard to analysis and pre-analysis. Care is to be taken that no contaminations occur during sampling, either from transport containers or from working clothes. In particular, spontaneous urine samples must be given at the end of the shift after changing into street clothes.

Intake of the ubiquitous nickel comes mainly via food consumption. Therefore, the excretion of nickel can be influenced by eating habits, involving foods with either a high or a low nickel content. Especially high nickel contents are found for example in nuts and almonds, various cereals and foods prepared from them (whole grain products, breakfast cereals), legumes, soy beans, lentils, seeds, sunflower seeds, poppy seeds, linseed, and so on, as well as chocolate or chocolate products. But also cabbage varieties, sea food and the internal organs of animals can contribute to the ingestion of nickel by humans (UBA 2001).

In humans, food supplements such as seaweed products (algae) result in a nickel intake which is not to be neglected. On the other hand, kitchen untensils containing nickel apparently have no influence on the amount of nickel excreted with the urine. The renal excretion of persons suffering from nickel dermatitis is also not increased. The influence of smoking habits on nickel excretion in urine is assessed differently.

From a review by Grandjean (1984) it can be seen that the amount of nickel inhaled by non-smoking city inhabitants is 0.2–1 µg/day (mean value < 0.4 µg/day). This means that non-smokers absorb only between 0.1% and 1% of the total amount of nickel with the inhaled air. In cigarette smokers, an additional intake of up to 4 µg nickel per smoked pack of cigarettes is obtained. Hence, from smoking, more nickel is taken up than from the atmospheric nickel intake.

Investigations by Stojanović et al. (2004) have shown that, for smokers, significantly higher renal nickel excretions (< 0.01–8.2 µg/l, median 1.2 µg/l) are obtained than for non-smokers (< 0.01–4.6 µg/l, median 0.5 µg/l).

In 163 women, Schwegler et al. (2009) found that an increased nickel exposure occurs in combination with increasing age, with the ingestion of food supplements, from drinking what is termed as stagnated drinking water, and after consuming food with high nickel content.

No publications are available giving concrete values as regards the concentrations of nickel in urine at which acute toxicity may be expected. However, it is to be assumed that, even if the BAR is repeatedly exceeded, this should not be accompanied by acute toxic effects.

The BAR relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3.0 g/l. In addition, the Commission considers selecting a more restricted target range of 0.5–2.5 g/l for urine samples to be useful, as this further improves the validity of the analyses undertaken. As a rule, in urine samples outside the limits cited above, a repetition of the analysis in normally hydrated test persons is recommended (see BAT Documentation 2010, translated).

6 References

Angerer J, Lehnert G (1990) Occupational chronic exposure to metals. II. Nickel exposure of stainless steel welders – biological monitoring. *Int Arch Occup Environ Health* 62: 7–10

Angerer J, Schaller KH, Fleischer M, Arbeitsgruppe "Analysen in biologischem Material" (1983) Nickel. In: Angerer J, Schaller KH, Henschler D (Eds.) Analytische Methoden zur Prüfung gesundheitsschädlicher Arbeitsstoffe. Band 2: Analysen in biologischem Material. 7. Lieferung, VCH, Weinheim

Goullé JP, Mahieu L, Castermant J, Neveu N, Bonneau L, Lainé G, Bouige D, Lacroix C (2005) Metal and metalloid multi-elementary ICP-MS validation in whole blood, plasma, urine and hair. Reference values. *Forensic Sci Int* 153: 39–44

Grandjean P (1984) Human exposure to nickel. In: Sunderman FW, Aitio A, Berlin A, Bishop C, Buringh E, Davis W, Gounar M, Jacquignon PC, Mastromatteo E, Rigaut JP, Rosenfeld C, Saracci R, Sors A (Eds.) Nickel in the human environment, IARC Scientific Publications, Vol. 53, 469–485

Heinrich R, Angerer J (1986) Analysenverfahren für physiologische und expositionsbedingte Konzentrationen – Cobalt und Nickel in biologischem Material. In: Welz B (Ed.) Fortschritte in der atomspektrometrischen Spurenanalytik, Band 2, VCH, Weinheim

Heitland P, Köster HD (2004) Fast, simple and reliable routine determination of 23 elements in urine by ICP-MS. *J Anal At Spectrom* 19: 1552–1558.

Heitland P, Köster HD (2006 a) Biomonitoring of 37 trace elements in blood samples from inhabitants of northern Germany by ICP-MS. *J Trace Elem Med Biol* 20: 253–262

Heitland P, Köster HD (2006 b) Biomonitoring of 30 trace elements in urine of children and adults by ICP-MS. *Clin Chim Acta* 365: 310–318

Herber RFM (1999) Review of trace element concentrations in biological specimens according to the TRACY protocol. *Int Arch Occup Environ Health* 72: 279-283

Mundt-Becker W, Angerer J (1981) Ein praxisgerechtes atomabsorptionsspektrometrisches Verfahren zur Bestimmung von Nickel im Harn. *Int Arch Occup Environ Health* 49: 187–192

Schaller KH, Angerer J, Drexler H (2002) Quality assurance of biological monitoring in occupational and environmental medicine. *J Chromatogr B* 778: 403–417

Schwegler U, Twardella D, Habernegg R, Fromme H, Darsow K, Federov M, Behrendt H, Schaller KH (2007) Pilotprojekt zur Erfassung der inneren Nickelbelastung weiblicher Patientinnen einer dermatologisch-immunologischen Klinik. *Gesundheitswesen* 69: 192

Schwegler U, Twardella D, Fedorov M, Darsow U, Schaller KH, Habernegg R, Behrendt H, Fromme H (2009) Innere Nickelbelastung von dermatologischen Patientinnen. *Gesundheitswesen* 71: 399–404

Stojanović D, Nikić D, Lazarević K (2004) The level of nickel in smoker's blood and urine. *Cent Eur J Publ Health* 12: 187–189

UBA (Umweltbundesamt) (2001) Nickel. Stellungnahme der Kommission "Human-Biomonitoring" des Umweltbundesamtes. *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 44: 1243–1248

Wilhelm M, Ewers U, Schulz C (2004) Revised and new reference values for some trace elements in blood and urine for human Biomonitoring in environmental medicine. *Int J Hyg Environ Health* 207: 69–73

Wrbitzky R, Göen T, Letzel S, Frank F, Angerer J (1995) Internal exposure of waste incineration workers to organic and inorganic substances. *Int Arch Occup Environ Health* 68: 13–21

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Approved by the Working Group: 26 January 2009