Arsenic trioxide

EKA

The correlation between external and internal exposure yields the following data:

Air Arsenic trioxide mg As/m^3	Urine Arsenic µg As/l
0.01	50
0.05	90
0.10	130

Sampling: end of exposure or end of shift after several consecutive shifts

Date of evaluation 1993

Synonyms –

Formula As_2O_3

Molecular weight 197.84

Melting point
amorphic or glassy form 312.3 °C
crystalline cubic form 274.0 °C

Solubility in water
amorphic or glassy form 37 g/l (20 °C)
crystalline cubic form 18 g/l (20 °C)

MAK [last established: 1975] Carcinogenic substance: Category III A1 of the MAK and BAT Values List

TRK [1993] 0.1 mg/m^3 (calculated as arsenic in total dust) for arsenic trioxide and pentoxide, arsenous acids, arsenic acid and its salts (arsenites, arsenates)

In 1986 the working group "Setting of Threshold Limit Values in Biological Material" of the DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area published a relationship between the arsenic concentration in the air and the level of arsenic excretion in biological material for exposure to arsenic

trioxide at the workplace (Exposure Equivalents for Carcinogenic Working Materials, EKA). The volatile arsenic compounds in the urine sample which can be determined after direct hydrogenation were defined as the arsenic excretion in urine. These are inorganic arsenic and its products of metabolism monomethylarsonic acid and dimethylarsinic acid. The correlation determined between the external and internal exposure is based on the data from two field studies (31, 36).

The TRK value valid at the time of the evaluation was 0.2 mg/m^3. Not least thanks to a publication by the working group "Setting of Threshold Limit Values in Biological Material" the TRK value was reduced in 1988 to 0.1 mg/m^3 (39).

In the meantime the availability of new scientific data allows reassessment of the relationship between external and internal exposure to arsenic. Of particular relevance is a study on the external and internal exposure to arsenic trioxide by Offergelt et al. (30). Arsenic concentrations in the air are shown to correspond to lower renal excretion levels than described in the relationship between exposure equivalents. The reasons for this difference include the fact that the method of determination of arsenic in the air at the workplace used to ascertain the external exposure has been improved. A method published by the ISO allows the efficient determination of arsenic trioxide dusts and fumes in the air. This is achieved by the use of specifically prepared filters. It can be assumed that in most previous investigations the published arsenic concentrations in the air were too low with the consequence that the arsenic excretion levels given in the correlation tables should be assigned to higher air concentrations.

This new data from the literature and the improvements in the methods make a re-evaluation of the EKA values for arsenic excretion in urine necessary.

1 Metabolism and Kinetics

Arsenic compounds can be taken up by man both via the lungs and also via the gastrointestinal tract. At the workplace inhalation is the dominant route of absorption. It should be borne in mind that in addition to inhalation, gastrointestinal absorption of arsenic from contaminated hands must also be assumed to take place (36).

The pulmonary deposition of inhaled arsenic compounds is above all determined by the size of the particles (32, 34). Non-inspirable particles are transferred with the mucous into the gastro-intestinal canal. From there, transfer of arsenic trioxide or the arsenic acid via the intestinal mucous membranes to the blood and lymph vessels is possible (34). The absorption in the lungs depends to a great extent upon the solubility of the arsenic compounds. Foa et al. (18) have suggested that pulmonary clearance is biphasic. 75 % is eliminated with a half-time of four days, 25 % with a half-time of ten days. Studies on persons who were investigated 2 to 19 years after the end of exposure provided indications of considerably longer retention times (8).

Gastrointestinal absorption is the most important route of absorption of arsenic from non-occupational exposure. Absorption takes place above all with food, in particular when sea-food is eaten, and with drinking water. The absorption of inorganic arsenic compounds from the gastrointestinal tract is determined mainly by the solubility of the compounds. The proportion of the dose absorbed in humans is more than 90 % if water-

soluble compounds are ingested. In the case of arsenic trioxide which is only slightly soluble in water the gastro-intestinal absorption is slower and depends on the size of the particles and the pH of the hydrochloric acid in the stomach. Organic arsenic compounds from sea-food are almost completely absorbed after ingestion (18).

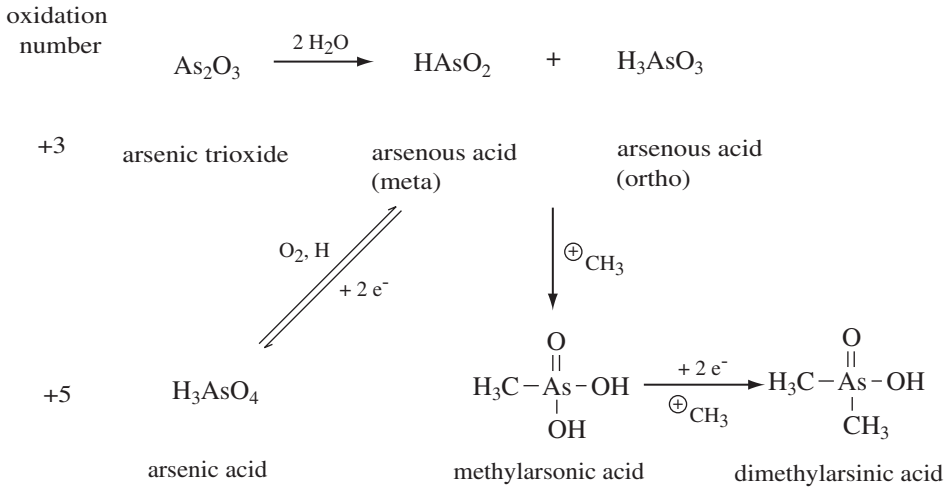

Fig. 1: Metabolism of arsenic trioxide in mammals and humans; metabolites in the urine: arsenic (III), arsenic (V), methylarsonic acid (MA) and dimethylarsinic acid (DMA)

The metabolism of arsenic in the human organism is shown in figure 1. Animal experimental and human investigations have shown that arsenic (III) is metabolised to arsenic (V), monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA). The main metabolite is dimethylarsinic acid which accounts for 50 – 80 % of the urinary metabolites. It is in principle true that occupationally exposed persons show the same spectrum of metabolites as non-exposed persons. However, there are quantitative differences which depend on the level of exposure. After high exposures the metabolism to dimethylarsinic acid decreases which is probably to be interpreted as a saturation of the methylation process (5, 6, 15, 24). Methylation is the most important natural detoxification mechanism. Both monomethylarsonic acid and dimethylarsinic acid are less toxic than the inorganic acid.

Organoarsenic compounds such as occur in food are not biologically transformed and thus form no inorganic or methylated arsenic compounds in the human organism.

Buchet et al. (4) investigated the changes with time in the concentration of arsenic metabolites in the urine after ingestion (3 persons) of 6.67 µmol sodium arsenate (III). The total arsenic content was determined by dry ashing, the metabolites arsenous acids and arsenic acid as well as monomethylarsonic acid (MMA) and dimethylarsinic acid (DMA) according to a modified method from Braman et al. (7). After one day, 22 % of the dose had been excreted, 38 % in the form of inorganic arsenic, 23 % as MMA and 39 % as DMA. After four days, 50 % of the arsenic taken up had been excreted with the urine, whereby the proportion of inorganic arsenic was reduced to 11 % and that of dimethylarsinic acid had increased to 76 %. After 14 days the persons showed normal arsenic values.

Mappes (26) obtained the following results after ingestion of 13.40 µmol arsenic trioxide in an experiment on himself: 52 % of the arsenic taken up had been excreted in the urine after 24 hours. Pharmacokinetic investigations demonstrated that for arsenic trioxide there are two different compartments.

2 Critical Toxicity

Chronic arsenic intoxication is of importance from an occupational medical point of view. A detailed description of the symptoms can be found in the occupational-medical toxicological documentation of the MAK value (19) as well as in Landrigan (22), Arnold (3) and Vahter (35).

Due to its carcinogenic properties in humans, arsenic trioxide as well as arsenic pentoxide, arsenous acid, arsenic acid and its salts have been classed in category A1 of section III "Carcinogenic Substances" of the MAK and BAT Values List (13). A review of the human carcinogenicity can be found in the documentation of the IARC (21) and the WHO (38).

3 Exposure and Effects

The DFG Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area have given their detailed opinion on the question of the body burden and effect on persons occupationally exposed to arsenic trioxide both in the occupational-medical toxicological documentation of MAK Values and also in the publication by Wichmann and Lehnert (39). Due to the carcinogenic effects of inorganic arsenic in man the chronic effects of arsenic cannot be used to evaluate a threshold limit value.

Enterline found in an epidemiological study a significant linear relationship between the standardised mortality ratio (SMR) for lung cancer and the renal arsenic excretion (14). On the basis of the regression equation of SMR = 86.1 + 0.590 As in urine (µg/l) the SMR for an arsenic concentration in the urine of 100 µg/l is 145, for 500 µg/l the SMR is 380.

The US American BEI documentation (2) is based on the relationship between internal exposure, determined as arsenic excretion in the urine, and the corresponding effects on health. As relevant effects peripheral neuropathy, peripheral angiopathy and liver and kidney function disorders are listed.

4 Selection of the Indicators

After exposure to inorganic arsenic there is a significant and specific increase in the arsenic species monomethylarsonic acid, dimethylarsinic acid and inorganic arsenic excreted in the urine. The *determination* of these three arsenic species *in the urine* is therefore the preferred method for the biological monitoring of workers who are exposed

to inorganic arsenic. The measurement of these species of arsenic is not influenced by organic arsenic compounds taken up with food.

Inorganic arsenic and its metabolites are rapidly excreted after the beginning of exposure. The urine concentration increases slowly and remains at a relatively constant level during the first days of exposure. During the working day and from the end of work to the beginning of the next shift there are no great changes in the concentration (30, 36). The elimination kinetics result in a significant accumulation of arsenic and its metabolites during the working week. Sampling should therefore take place at the end of the working week.

The determination *of arsenic in blood* is of no importance in the biological monitoring of occupationally exposed persons (22, 28). The reason for this is that the biological half-life in blood both for inorganic and organic arsenic is relatively short. This means that the blood concentration is only at an increased level for a short time after absorption. Furthermore, there are no routine methods available for the specific determination of inorganic arsenic and its metabolites in blood.

The arsenic concentrations in *hair and finger nail samples* are usually higher than in other compartments of the human organism. The reason for this is the high content of cystine whose thiol groups bind trivalent inorganic arsenic. The measurement of the arsenic content of hair and finger nail samples has not acquired any importance in occupational medical practice, the reasons being the non-standardised sampling, difficulties in analysis as well as a considerable danger of contamination. Moreover, there are no relevant studies for the evaluation of threshold limit values.

5 Methodology

Inorganic and organic arsenic compounds in urine are transformed for quantitative measurement into volatile hydrides and determined by atomic absorption spectroscopy (hydride method) (16, 17). Using the method of direct hydrogenation of a urine sample only inorganic arsenic compounds and their metabolites monomethylarsonic acid and dimethylarsinic acid are transformed into volatile hydrides and quantified. Organic arsenic compounds, which are taken up during consumption of sea-foods and excreted renally, are not determined (29, 37). A tested method can be found in the loose-leaf collection “Analysen im biologischen Material” (20) and in its English edition “Analyses of Hazardous Substances in Biological Materials” (1).

If the urine sample is digested wet or dry the total arsenic content is determined. Therefore wet or dry digestion should not be carried out.

The following explanations refer to the measurement of inorganic arsenic and its metabolites. In biological monitoring this “arsenic fraction” should be measured. Table 1 gives an overview of the published data for non-exposed persons. Only studies which distinguish between the various arsenic species were taken into account. Column Σ shows the "fraction" determined by the hydride AAS method.

Tab. 1: Arsenic values in the air and urine in non-exposed persons and percentage distribution of the various arsenic species

Air	Urine							Literature
(µg As/m³)	As (III) (µg/l)	As(V) (µg/l)	Methylarsonic acid (MA) (µg/l)	Dimethylarsinic acid (DMA) (µg/l)	Σ As (III), As (V), MA, DMA (µg/l)	Total As (µg/l)	spec. weight urine	
	8.4 % 1.9	17.3 % 3.9	8.0 % 1.8	66.4 % 15.0	100 % 22.6	–	–	4[1)]
			3.6 ± 2.4	15.5 ± 6.8				4[2)]
	6 % 3.7 ± 1.4 6 %	5 % 3.0 ± 1.3 5 %	20 % 11.3 ± 5.3 19 %	68 % 39.2 ± 18.2 67 %	100 % 57.3 ±21.3 98 %	58.4 100 %	1.024	48[3)]
3.6 ± 1.56 [a)]	7 % 1.3 ± 1.58 6 %	7 % 1.3 ±1.59 6 %	19 % 3.4 ±1.63 16 %	66 % 11.5 ± 1.47 54 %	100 % 17.5 [b)] 83 %	21.2 100 %	1.018	38[4)]
	11 % 1.6 ± 1.2 11 %		12 % 1.7 ± 1.2 11 %	77 % 11.2 ± 5.9 74 %	100 % 14.5 ± 7.5 [a)] 96 %	15.1 [b)] 100 %	–	6 [5)]

[1)] n = 4.3 ♂ + 1 ♀, 34 ± 7.8 years

[2)] x ± s, n = no data

[3)] Ibd. p. 51, Tab. 2, x ± s, n = 20; total arsenic was calculated on the basis of a given correlation: $y_{\text{wet digestion}}$ (µg/l) = 0.915 · $x_{\text{separation method}}$ (µg/l) + 6

[4)] a) geom. mean ± s, 56 % <1.2 µg/m³ (detection limit), n = 41; urine values: geom. mean ± s, n = 41; b) calculated; total arsenic determined by wet digestion

[5)] Ibd. p. 22, Tab. 10, x ± s, n = 5; a) calculated b) dry ashing; geom. mean because an outlier is included (arithm. mean 18.7 ± 14.3)

As the measurement of arsenic in the air is also of great importance for the evaluation of a correlation between the external and internal exposure the method is briefly described here. The determination of arsenic in particle and vapour form should take place according to the sampling method AGSA-AA I No. 15-90 of the ISO. Cellulose acetate membrane filters impregnated with sodium carbonate and glycerine are used as sampling phases. The filters prepared in this way guarantee an extremely efficient separation of the arsenic compounds, independent of the state of aggregation (10, 30). For the quantitative determination of arsenic the filters are digested by wet oxidative digestion and the arsenic quantified using hydride AAS or GF-AAS. This method represents the present state of the art.

6 Background Exposures

Arsenic can be taken up by man in drinking water, food and from the air. Food is the main route of absorption. Food, with the exception of sea-food, contains less than 0.25 mg arsenic/kg; various kinds of fish between 1 and 10 mg/kg and shell fish more than 100 mg/kg. In food of maritime origin the arsenic is in organic form (arsenobetaines and arsenocholines). The daily uptake via food is estimated to be between 0.04 (without fish) and 0.19 mg arsenic (with fish). The daily arsenic uptake via the drinking water and the air is not significant.

With the hydride AAS method suggested in chapter 5 the aromatic arsenic compounds excreted unmetabolised in the urine are not determined. Under these conditions of measurement the "normal" arsenic excretion is below 25 µg/l (see also Tab. 1). Thus, it must be ensured that the above-mentioned method of analysis is used for the monitoring of persons occupationally exposed to arsenic. After the digestion of urine samples and the consumption of crustaceans arsenic can be measured in the urine in the mg range.

7 Evaluation of the Biological Exposure Equivalents for Carcinogenic Substances (EKA)

Various field studies on humans can be referred to for the evaluation of correlations between the external arsenic exposure and the renal excretion of arsenic. The correlation evaluated in 1986 is based mainly on two studies (31, 36).

The meaningfulness of the field study carried out by Pinto et al. (31) on 24 workers from a smelting works is limited by the fact that the total arsenic excretion in the urine was analysed without any further specification. It was checked anamnestically that no fish was eaten in the period of investigation. Nevertheless, it cannot be excluded that the results were influenced by the uptake of organoarsenic compounds. Furthermore, it must be assumed that the arsenic concentrations given for the air were too low as arsenic oxide vapours were probably not determined.

This assumption also applies to the study by Vahter et al. (36). According to investigations by Costello et al. (10) only approx. 42 % of the arsenic trioxide in the vapour phase is determined when untreated cellulose acetate filters are used. There was a highly significant correlation of r = 0.92 between the arsenic concentration in the air measured by personal air sampling and the renal excretion of organic arsenic and its metabolites (36). However, with four persons the urinary excretion values were much greater than were to be expected from the external exposure. The authors suspected that the persons had been exposed to arsenic taken up directly from contaminated hands, cigarettes or snuff. Therefore this study was not included in the present evaluation.

The study carried out by Landrigan et al. (23) was also not included in the evaluation. This working group investigated 48 lead battery workers who were exposed both to arsine and arsenic trioxide. According to the currently available data it seems that the relationship between the arsenic content of the air and the renal excretion of inorganic arsenic and its metabolites is influenced by the chemical form of the arsenic species at the workplace. It is known e.g. that lead arsenate, calcium arsenate, gallium arsenide and to a certain extent arsenic trisulphide are absorbed more slowly in the lungs than arsenic trioxide. Arsine, however, is absorbed considerably better than arsenic trioxide. Due to this mixed exposure and the fact that the total arsenic content of the urine was determined, this study can also not be used for the evaluation.

Roels at al. (33) investigated persons exposed to arsenic in a glass factory. As, on the one hand, only a small fraction of the dust was able to enter the alveoli and, on the other, the urinary excretion levels were relatively high, the authors assumed that oral uptake from contaminated hands had had a considerable influence on the results.

The studies described below were taken into account for the evaluation of the EKA value. The data presented there are used for the compilation of table 2.

Tab. 2: Calculated arsenic concentration in the urine (arsenic, inorganic and metabolites) at various arsenic concentrations in the air at the workplace

	Arsenic concentrations in the air (mg/m^3)			
Study	0.01	0.05	0.10	Reference
82 smelters As_2O_3 exposure	25 µg/l	76 µg/l	139 µg/l	Smith 1977
28 smelters As_2O_3 exposure	44 µg/l	101 µg/l	127 µg/l	Enterline 1987
11 smelters As_2O_3 exposure	68 µg/l	102 µg/l	146 µg/l	Yamauchi 1989
22 employees of sulphuric acid production Exposure to As_2O_3 dust and fumes	30 µg/g creatinine	54 µg/g creatinine	69 µg/g creatinine	Offergelt 1992

In a comprehensive study Smith et al. (34) investigated the excretion of inorganic arsenic and its metabolites in the urine of 82 smelters employed in a copper works. The external exposure was determined by personal air sampling, urine sampling took place in the morning on two consecutive days. There was a statistically significant correlation between the external exposure and the concentration of various arsenic species in the urine. A regression equation was only given for the relationship between the arsenic in the air and the dimethylarsinic acid excretion in urine. As dimethylarsinic acid represents approx. 65 % of the arsenic metabolites and the ratio of the arsenic species to one another was relatively constant and independent of the exposure concentration, for the fraction inorganic arsenic and its metabolites in the urine a concentration of about 70 µg/l can be estimated for external exposure to 50 µg/m^3. In addition the authors quoted values for external and internal exposure for four exposure groups:

	Arsenic in air	Arsenic in urine
Controls	3.6 µg/m^3	17.5 µg/m^3
Group with low-level exposure	8.3 µg/m^3	25.7 µg/m^3
Group with medium-level exposure	46.1 µg/m^3	49.6 µg/m^3
Group with high-level exposure	52.7 µg/m^3	96.6 µg/m^3

The data yields the following relationship as a linear regression:

Arsenic in urine (µg/l) = 12.6 + 1.26 arsenic in air (µg/m^3)

Within the framework of an epidemiological study of the frequency of lung cancer in the workers of a copper smelting works, a relationship between urine excretion and external exposure was established. The relationship was not linear: arsenic in urine [µg/l] = (arsenic in air [µg/m^3]/0.0064)$^{0.515}$. The measurements were based on stationary air sampling (14).

Yamauchi et al. (40) published in 1989 a field study on 37 gallium arsenide workers and 11 smelters. The air concentrations measured by stationary air sampling were associated with urine values which resulted from two urine collections on 2 to 3 days. For gallium arsenide there were only small increases in the arsenic excretion. This can be attributed to the fact that gallium arsenide can only be absorbed by the human organism to a very small extent (35, 40). For the smelters who were exposed to arsenic trioxide an average urine excretion of inorganic arsenic and its metabolites of 239 µg/l was associated with an average air concentration of 0.336 mg/m .

In a field study that was published in 1992 by Offergelt et al. (30) 18 workers of a company producing sulphuric acid were investigated. The arsenic concentration in the breathing zone was determined by the sampling and analysis method described above. The air measurements took place during five days, the urine samples were collected after the shift and before the next shift. In biological material the inorganic arsenic as well as the monomethylarsonic acid and the dimethylarsinic acid were measured selectively. For 82 pairs of values there was a significant correlation of r = 0.48. The regression equation was log arsenic in urine (µg/g creat.) = 1.130 + 0.353 log arsenic in air (µg/m^3).

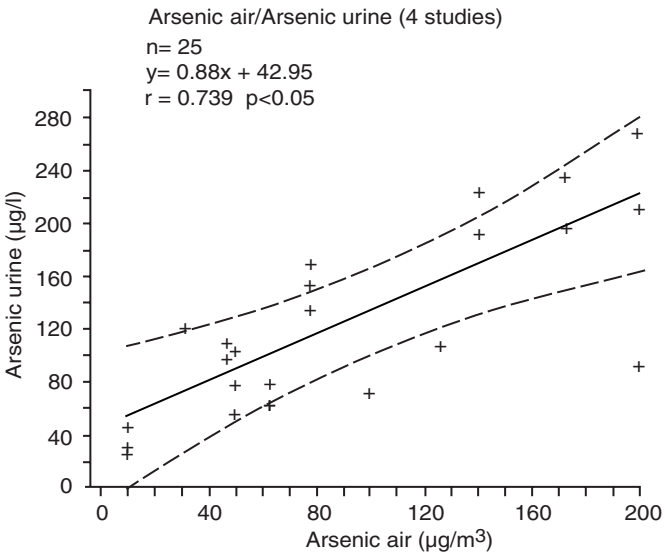

Fig. 2: Correlation diagram for the relationship between the arsenic concentration in the air and the renal arsenic excretion on the basis of the four studies used for the evaluation of the EKA values

Table 3 shows the arsenic excretion (inorganic arsenic + metabolites) in the urine extrapolated for various arsenic concentrations in the air. The post shift values as well as the values before the next shift were taken into consideration.

The arsenic excretion levels in the urine listed in table 2 for defined arsenic concentrations in the air are calculated from linear and non-linear relationships between the data for the external and internal exposure. With the exception of the study by Enter-line et al. (14), in which the arsenic fraction measured was not described, the urine excretion levels are based on the measurement of inorganic arsenic and its metabolites.

The correlates calculated show a high variance. This wide range can be explained, on the one hand, by the different methods of sampling and analysis of arsenic in the air. On the other hand the extrapolation from low external exposures to higher ones is critical with this database. As a rule the external exposures in the studies listed are below 0.05 mg/m^3. In the lower exposure range (0.01–0.05 mg/m^3) the calculated values correspond better than those in the upper range.

The lowest excretion values are to be found in the study by Offergelt et al. (30) in which great importance was laid on an exact and complete determination of the arsenic in the air. For a period of five days the external exposure was determined with a method of sampling and analysis recommended by the ISO, with personal air sampling during the whole of the shift. Of the persons investigated no-one wore personal breathing protection. An oral uptake of arsenic can be largely excluded. The arsenic levels in the urine measured at the end of the shift do not differ greatly from those in the urine samples which were collected before the next shift (see Tab. 3). The individual range of variation of the arsenic excretion is, however, considerable. It can be seen in table 3. The largest values measured in the lower range of exposure correspond in their order of magnitude with the extrapolated values from the other studies.

Tab. 3: Calculated renal arsenic excretion (inorganic arsenic and its metabolites MA + DMA) in the urine samples collected post-shift and before the next shift in relation to the arsenic concentration in the air at the workplace with exposure to As_2O_3 dusts and fumes (30)

Arsenic in air (mg/m^3)	Renal arsenic excretion (µg/g creatinine)	
	after the shift	before the next shift
0.0125	33 (26–42)	31 (24–40)
0.025	42 (36–50)	39 (33–47)
0.050	54 (47–62)	50 (43–58)
0.100	69 (56–84)	64 (52–79)
0.200	88 (65–117)	81 (60–111)
0.400	112 (75–166)	104 (68–158)

The results are given as geometric means with 95 % confidence intervals

The evaluation of the EKA values takes place on the basis of the four selected studies. The correlation analysis yields the relationship between air and urine values shown in figure 2. Only the data up to an external exposure to 0.20 mg/m^3 are included. The arsenic excretion in the urine (inorganic arsenic and metabolites) was determined by interpolation for external exposures of 0.01, 0.05 and 0.1 mg/m^3. The relationship between the arsenic concentration in the air at the workplace and the arsenic excretion in the urine is shown below:

Air Arsenic concentration	Urine Arsenic concentration
0.01 mg/m^3	51 µg/l
0.05 mg/m^3	87 µg/l
0.10 mg/m^3	131 µg/l

With regard to the criticism of the studies used, discussed in detail above, this correlation should be regarded as provisional.

8 Interpretation of the Data

Pretreatment of urine samples by wet or dry ashing techniques permits determination of the total arsenic content of the urine. In this way the arsenic taken up with food is included. In particular fish and other sea-foods contain high levels of organic arsenic compounds (9, 25, 27) which are quickly absorbed and excreted via the kidneys (11, 12). This can lead to a great increase in the total arsenic content of the urine (4, 17, 25, 37). For this reason pretreatment by wet or dry ashing should not be carried out.

The method of direct hydrogenation of the urine sample should be used. Even with this procedure it was observed that after ingestion of sea-food there is an increase in the level of arsenic compounds. The increase is small and can amount to 12 µg As/l urine (29, 37).

Occupational medical health examinations on persons exposed to inorganic arsenic must be carried out according to the berufsgenossenschaftlicher Grundsatz G 16 (guideline issued by the Employers' Liability Insurance Association).

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