Addendum to Mercury and Its Inorganic Compounds

BAT	30 µg Hg/l urine Sampling time: not fixed
Date of evaluation	2005
MAK value (1970)	0.1 mg/m^3
Skin absorption	–
Sensitizing effect (1999)	Sh
Carcinogenic effect (1999)	Category 3B

10 Re-evaluation of the BAT Values

A BAT documentation is available from 1997 in which the BAT values were established at 100 µg Hg/l urine and 25 µg Hg/l blood (see BAT documentation 1997). The last addendum for the MAK value was published in 1999 (Greim 1999).

Since the last BAT documentation, new studies have been published, particularly on the neurotoxic and nephrotoxic effects of mercury which make a re-evaluation necessary.

10.1 Metabolism and toxicokinetics

To determine the toxicokinetics of mercury vapours, 9 volunteers were exposed for 15 minutes to median mercury vapour concentrations of about 0.4 mg/m^3 (range 0.365–0.430 mg/m^3) under light physical exercise. The median mercury retention was 69 % of the inhaled dose. During the first three days after exposure, 7.5 % to 12 % of the absorbed dose had been eliminated via exhalation; the half-life was 2 days. In the plasma, the median value of the half-life in the second phase was about 10 days. The amount of mercury eliminated with the urine was 1 % on the first day and up to 40 % after 30 days. In volunteers, the half-life values of mercury in urine greatly varied and were between 12.8 and 98.9 days, with a median of 63.2 days (Jonsson et al. 1999; Sandborgh-Englund et al. 1998).

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10.2 Exposure and effects

10.2.1 Nephrotoxicity

The cross-sectional studies of nephrotoxic effects published since the BAT documentation of 1997 are summarized in Table 1. No publications on longitudinal studies are available.

Cross-sectional studies

Investigations in persons with amalgam fillings

Mortada et al. (2002) compared 49 non-smokers with an average of 4.4 amalgam fillings, who were found to have a concentration of 1.79 µg Hg/g creatinine (about 2.2 µg Hg/l urine), with 52 non-smokers without amalgam fillings selected according to age and socio-economical status. In the patients with amalgam, the parameters for N-acetyl-β,D-glucosaminidase (NAG), γ-glutamyl transpeptidase (γ-GT) and albumin were significantly increased. All of the increased mean values of enzymes in the patients with amalgam were above the standard deviation of the controls, indicating relevant kidney changes in persons with amalgam. As the amount of mercury to which the amalgam group is exposed is very low, however, and as no changes in kidney enzymes can be observed at such mercury levels in the studies on exposed workers, it is very questionable whether the kidney changes can be attributed to mercury exposure from the amalgam fillings or to other factors. Therefore, this study will not be considered when establishing the BAT value.

Investigations in dental medical personnel

Rojas et al. (2000) demonstrated that, in 22 dentists, the activity of NAG in urine was increased slightly but not in a statistically significant manner at 2.9 ± 3.0 units/l which, in comparison, was lower than the values of 5.2 ± 8.1 units/l measured in the 15 assistants. In both denstists and dental assistants, the concentrations in urine were 22 µg Hg/g creatinine (about 26 µg Hg/l urine). No control population was investigated. As the mercury exposure level of both groups was the same, it can be assumed that the slight differences in NAG activity may be attributed to other factors.

Investigations in industrial workers

In 122 workers with mean concentrations of 8.1 µg Hg/g creatinine in urine (about 9.7 µg Hg/l urine) (Alinovi et al. 2002) or in 38 workers with concentrations of 11.9 µg Hg/g creatinine (about 14.3 µg Hg/l urine) and maximum values of 35 µg Hg/g creatinine (about 42 µg Hg/l urine) (Camerino et al. 2002), no differences could be found in the kidney parameters investigated to those of the 197 and 47 controls, respectively.

Ellingsen et al. (2000a) reported on statistically significant differences in NAG activity in 47 workers with concentrations of 5.9 (1.1 to 16.8) nmol Hg/mmol creatinine (about 12.5 (2.3 to 35.7) µg Hg/l urine). No other kidney parameters in urine or in serum were changed. The differences in NAG activity between exposed persons (0.18 ± 0.09 U/mmol creatinine) and controls (0.14 ± 0.10 U/mmol creatinine) were however very

slight, which makes the biological relevance of the findings questionable, especially as the other kidney parameters investigated showed no significant differences.

El-Safty et al. (2003) investigated 20 non-smoking workers exposed for up to 11 years showing concentrations of 21.4 ± 15.9 µg Hg/g creatinine (26 ± 19 µg Hg/l urine), as well as 27 non-smoking workers with exposures of up to 10 years showing concentrations of 25.6 ± 19.3 µg Hg/g creatinine (31 ± 23 µg Hg/l urine), and 36 non-smoking control persons. Three corresponding groups of smokers were investigated at the same time. The non-smoking workers exposed to mercury showed changes in five different kidney parameters (total protein, retinol-binding protein, leucine aminopeptidase, glutathione transferase, NAG) accepted as being sensitive for mercury-related kidney effects. In smokers, the values were also increased without mercury exposure, and continued to increase with increasing mercury exposure.

In a Europe-wide study by Cárdenas et al. (1993) to determine the renal toxicity of different metals, 14 kidney parameters were measured in workers. In the case of mercury, no changes in kidney parameters were observed at urinary concentrations below 5 µg Hg/g creatinine (about 6 µg Hg/l urine). The first changes in parameters (prostaglandin PGE_2, $PGF_{2\alpha}$, thromboxane TXB_2) were recorded at concentrations between 5 and 50 µg Hg/g creatinine (about 6 to 60 µg Hg/l urine) (Price et al. 1996); significantly reduced eicosanoid concentrations, especially PGE_2, were already reported at 35 µg Hg/g creatinine (about 42 µg Hg/l urine) (Roels 2002; Roels et al. 1999). At concentrations of over 50 µg Hg/g creatinine (greater than 60 µg Hg/l urine), brush border antigens BB_{50}, BBA and HF5 and intestinal alkaline phosphatase were increased in particular. The Tamm-Horsfall glycoprotein (THG), NAG, BB_{50}, HF5 and intestinal alkaline phosphatase parameters were positively correlated with the mercury concentration in urine, although they showed no correlation with exposure duration (Price et al. 1996). Those parameters sensitive to mercury-related kidney changes (Taylor et al. 1997; Wedeen et al. 1999, see also below) are among those cited in particular.

In a study by Abdennour et al. (2002) on two groups of workers with a excretion of 29.3 ± 23.2 µg Hg/g creatinine and 138.6 ± 80.9 µg Hg/g creatinine (35.2 ± 27.8 µg Hg/l urine and 166.3 ± 97.1 µg Hg/l urine), higher numbers of workers with proteinuria (14.6 % and 39 %) were found as exposure increased when compared with the control group (4.9 %). The urinary pH value was frequently below 6.5, especially in the workers of the high-exposure group.

Further studies (often of an earlier date) confirmed that, in workers with mean concentrations in urine of 84.1 nmol Hg/l (16.9 µg Hg/l) with a maximum value of 260 nmol Hg/l (52 µg Hg/l), no changes in the albumin and NAG values were found in urine (Piikivi and Ruokonen 1989). Changes in kidney parameters are to be observed at concentrations in urine of above 50 µg Hg/l (Barregård et al. 1988; Buchet et al. 1980; Ehrenberg et al. 1991; Himeno et al. 1986) or above 100 µg Hg/l, respectively (Kolenič et al. 1994, 1997; Marek and Wocka-Marek 1994). One investigation reports indications of changes in kidney parameters at concentrations below 50 µg Hg/l urine (Foà et al. 1976). As, however, in these investigations, only one kidney parameter was usually measured, they are not described in further detail here.

Adversity of nephrotoxic effects

All forms of mercury are nephrotoxic, and inorganic forms have a greater acute effect than organic forms. Kidney damage from inorganic mercury compounds manifests itself to full extent within 24 hours after exposure. Inorganic mercury is taken up by the kidneys, where it accumulates. Within the kidneys, the pars recta of the proximal tubuli constitutes the most sensitive segment as regards the toxic effect. Here, interactions occur between mercury ions and the thiol groups of protein, peptides and amino acids. The interactions with albumin, metallothionein, glutathione and cysteine are of particular importance. As a result of the toxic effects, kidney cells are damaged, cellular enzymes and proteins are released into the tubular lumen, from where they are excreted with the urine (Zalups 2000).

When interpreting such changes, the question is important whether the different biomarkers indicate adverse nephrotoxic effects.

The spectrum of the indicators for kidney damage comprises a wide range of parameters, which may be classified as follows (Price et al. 1996, Wedeen et al. 1999):

1. High molecular proteins, e.g. albumin, immunglobulin G (IgG), transferrin
2. Low molecular proteins, e.g. β_2-microglobulin (β_2M), α_1-microglobulin, retinol-binding protein (RBP)
3. Lysosomal proteins (enzymes), e.g. N-acetyl-β,D-glucosaminidase (NAG), glutathione transferase (GST)
4. Brush border enzymes, e.g. alanine aminopeptidase, γ-glutamyl transpeptidase (γ-GT), intestinal alkaline phosphatase (IAP)
5. Distal tubular proteins, e.g. Tamm-Horsfall glycoprotein (THP)
6. Glomerular structural proteins, e.g. glycosaminoglycans (GAG)
7. Prostaglandins, e.g. PGE_2, $PGF_{2\alpha}$
8. Kallikrein (Kal)

In principle, increased excretion of high molecular proteins is more important for indication of serious kidney damage than molecular proteins or enzymes. More lysosomal enzymes are released from damaged tubular cells than from the circulation. A tubular proteinuria can also indicate a merely transitory effect. The evidence of biomarkers in urine is in the case of an exposure to mercury – contrary to cadmium – not a sufficiently reliable indicator of chronic renal damage (Wedeen et al. 1999). In the context of specificity, the results of investigations indicate that it is not the individual biomarker that shows a higher specificity, but specific patterns (Taylor et al. 1997). In the case of mercury, the following biomarkers are considered to be particularly sensitive: intestinal alkaline phosphatase, retinol-binding protein and brush-border-specific antigens (Taylor et al. 1997; Wedeen et al. 1999).

When interpreting the findings, physiological variability of the biomarker must also be taken into account. Both the intraindividual as well as the interindividual variability of the parameters is considerable; this means that an adverse toxic effect need not necessarily be taken into consideration, even in cases where statistically significant differences are found (Taylor et al. 1997).

Concluding assessment of data on nephrotoxicity

In a number of different studies, some of them of an earlier date, consistent changes in different mercury-relevant kidney parameters have been observed at mercury concentrations of 50 µg/l urine and above. No clear effects on kidney parameters were

measured in workers found to have concentrations in urine of up to 35 µg Hg/l (Ellingsen et al. 2000a) or 42 µg Hg/l urine (Alinovi et al. 2002; Camerino et al. 2002). In the study conducted by El-Safty et al. (2003), nephrotoxic changes were found in non-smoking workers after more than 11 years of exposure, with concentrations in urine of 26 ± 19 µg Hg/l urine and in non-smoking workers after 10 years of exposure with levels of 31 ± 23 µg Hg/l urine, respectively. From the mean values and the standard deviations reported in this study, it can be deduced that the effects occur at concentrations corresponding to the 95th percentile of about 40 or 50 µg Hg/l urine.

Thus, available data indicate that no relevant mercury-related nephrotoxic effects are to be expected at a concentration of 30 µg Hg/l urine when taking the 95th percentile into account.

10.2.2 Neurotoxicity

In the Section of the 1997 BAT documentation entitled Neurotoxicity, it was stated that no increased occurrence of relevant neurological effects could be observed at a urinary excretion of less than 100 µg Hg/l. This statement was principally based on findings from longitudinal studies. The findings from cross-sectional investigations which, in part, deviate from the former, only received a low grade of scientific validity. In the documentation for establishing limit values, the fact was given that, when taking the relevance for health of the neurophysiological, psychological and psychomotor findings into account, neurotoxic effects relevant to occupational medicine can only start occurring at repeatedly found concentrations above 100 µg Hg/l urine (see documentation 1997). Taking more recent data on neurotoxic effects (see Table 2) as well as a meta-analysis and an analysis on dose-effect relationships into account, this conclusion is now being revised.

Cross-sectional studies

Investigations in persons with amalgam fillings

In 550 adults with amalgam fillings, Factor-Litvak et al. (2003) found no correlation between neuropsychological test results and a concentration in urine of 1.7 µg Hg/g creatinine (about 2.0 µg Hg/l urine). As the mercury levels resulting from the amalgam fillings are within the background exposure of the general population, these studies are not suitable for deriving a BAT value for mercury.

Investigations in dental medical personnel

Echeverria et al. (1998) investigated dental medical personnel (n = 48) with mean current urinary concentrations of 0.89 and 1.07 µg Hg/l. Functions of attentiveness, motor performance and mood scores showed significant dose-effect correlations with actual exposure parameters, while symptom scores and verbal memory tests were correlated with previous exposures.

In an investigation conducted by Aydin et al. (2003), dental medical personnel (n = 43) with current exposures of 1.17 nmol Hg/mmol creatinine (2.5 µg Hg/l urine) reported more symptoms and showed a reduced performance in a memory test as compared with 43 control persons.

The dental medical personnel (n = 162) with mean current exposures of 5.5 µg Hg/l investigated by Ritchie et al. (2002) reported an increasingly restricted ability to

concentrate (25.9 % versus 9.4 % in controls), and showed less favourable group results versus 163 control persons in an attentiveness and a memory test respectively. Nevertheless, no relationship with mercury exposure could be detected here in a regression analysis after making adjustments for sex and age – the dental medical personnel concerned was on average 7 years older than the controls.

Langworth et al. (1997) investigated 22 dentists and 22 female dental nurses and found weak correlations between symptoms and mood scores with mercury concentrations. In those exposed, the concentration in urine was currently at 3.0 nmol Hg/mmol creatinine (a concentration of about 6.4 µg Hg/l urine). On average, the investigated persons had been employed for 20 years (range 8 to 35 years) in the same field. At the time of the investigation, however, working with amalgam only took up about 24 minutes per person and day.

Urban et al. (1999) compared the visual evoked potentials and nerve conduction velocity measurements of 36 dentists showing current excretion of 13.2 µg Hg/24 h (≈ µg/l) with employees (see below) and 46 control persons showing an excretion of 0.8 µg Hg/24 h (≈ µg/l). A change in amplitudes of the visual evoked potentials could be demonstrated in all exposed groups versus the control group, by contrast to which no differences between the groups could be demonstrated.

Bittner et al. (1998) summarized the original data for 230 persons from 6 studies involving dentists. Approximately half of the dentists were found to have concentrations of around 3 µg Hg/l urine, the other half around 25 µg Hg/l urine. The authors found a significant association between test results on intentional hand steadiness and the log-transformed urinary mercury content.

The importance of the results of investigations in dental medical personnel on the neurotoxicity of mercury is problematic for two reasons. On the one hand, dose-effect relations in cognitive performance parameters and experienced symptoms have been recorded even at current mercury exposure levels within the normal range of the general population (≤ 5 µg Hg/l urine); this especially applies to the results of Echeverria et al. (1998) and Langworth et al. (1997). On the other hand, the fact must be taken into account that the use of amalgam fillings has decreased due to substitution by alternative materials over recent years and that, where amalgam fillings are still being used, modern methods are minimizing mercury exposure. Short-term, relatively high mercury exposure levels must be assumed where older methods are used, particularly in the preparation of amalgam fillings (using liquid mercury) as well as in the insertion, polishing and removal of such fillings. Symptoms of poisoning have also been reported (see Langworth et al. 1997). As to how far, in the investigations reported above, the findings reported can be attributed to higher mercury exposure levels of an earlier date, or to other substances used in dental practices, is difficult to decide. The available studies on dentists or dental personnel are thus not suitable for deriving a BAT value.

Investigations in industrial workers

In a study involving 47 chloralkali workers, Ellingsen et al. (2001) described no significant group differences in comparison with the control group in the context of neuropsychological tests and self-reported subjective symptoms. In multiple linear regression analyses incorporating potential confounders, however, an association was found between reduced attention and memory performance parameters and the current blood content (20.7 nmol Hg/l blood), as well as between attention performance and the

average exposure level to mercury in urine over preceding years. The mean annual exposure was at 9 nmol Hg/mmol creatinine (about 19 µg Hg/l urine) with a range of 4.0 to 19.6 nmol Hg/mmol creatinine (about 8.5 to 42 µg Hg/l urine). As stated by the authors, the effects were slight and probably of no clinical relevance. Data on biological monitoring had been recorded since 1949. Maximum concentrations were obtained in 1983 at about 11 nmol Hg/mmol creatinine (about 18 µg Hg/l urine) with a 95 % confidence interval up to about 14 nmol Hg/mmol creatinine (23 µg Hg/l urine). The current urinary content was cited to be 5.9 nmol Hg/mmol creatinine (about 12.6 µg Hg/l urine) with a range of 1.1 to 16.8 nmol Hg/mmol creatinine (about 2.3 to 36 µg Hg/l urine). As the exposures were recorded over a considerable number of years in conjunction with consistent exposures at low concentrations (about 20 to 30 µg Hg/l urine), and due to a good methodical performance, this study is suitable for the derivation of a BAT value. The neurological tests showed, with the exception of slight effects of subclinical relevance, no adverse changes in the workers.

Lucchini et al. (2002, 2003) compared 122 workers who had been exposed to mercury for an average of 14.6 years with 196 control subjects. The mean current urinary concentration was 10 ± 6.9 µg/g creatinine (12.5 ± 8.3 µg Hg/l) (95^{th} percentile, 23.5 µg Hg/g creatinine, corresponding to about 28.2 µg Hg/l urine) in the exposed workers and 1.9 ± 2.8 µg/g creatinine (95^{th} percentile, 5.4 µg Hg/g creatinine, corresponding to about 6.5 µg Hg/l urine) in the controls. No details on earlier exposures were given. Significant effects were found in the exposed workers, both in group comparison as well as in regression analyses. Reduced motor coordination, aggravated tremor and reduced prolactin concentrations in the serum (neuroendocrine parameter) were correlated with the occupational exposure to mercury. Only the reduced serum prolactin concentrations correlated with the current urinary mercury concentration. Interpretation of these findings is difficult according to the authors. The relevance and adverse nature of the findings are not clear; here, too, no details on earlier exposures are cited. Hence, these findings cannot be used for establishing the BAT value.

Urban et al. (2003b) established differences in colour discrimination ability on comparing 24 male chloralkali workers with 24 male control subjects. Here, the Colour Confusion Index (CCI) was increased at 1.15 versus control at 1.04. The groups were comparable in the context of age. Because they are not so high in absolute terms, the significant differences in alcohol and nicotine consumption between the groups are not indicative of a causal relationship; this was demonstrated in regression analyses as well. The mean current concentration of the exposed group was 20.5 ± 19.3 µg Hg/g creatinine (about 24.6 ± 23.2 µg Hg/l), the mean exposure time was 14.7 ± 9.7 years. The authors concluded that mercury is able to induce subclinical impairment in colour discrimination ability. However, as the increase in CCI to 1.15 is not to be assessed as an adverse effect, these findings cannot be used for establishing the BAT value.

Urban et al. (2003a) compared the reaction to light stimuli provided during EEG measurements in 24 male chloralkali workers with 24 male control subjects. Flushed out mercury was used as a biomarker within 24 hours after administration of a chelating agent. The mean concentration was 64.3 ± 59.9 µg Hg/24 h (≈ µg/l assuming an elimination rate of 1 litre urine in 24 hours). The mean exposure time was 15 ± 9.7 years. The groups were comparable in the context of age. Significant group differences in electrophysiological activity were found as a result of light stimulation. In this study as

well, an influence of the significant differences in alcohol and nicotine consumption between the groups appears to be extremely improbable as a result of the absolute quantities taken up (e.g. 140 g alcohol per week). There were only hints of a dose-effect relationship could be established: it was possible to show that the changes in EEG in the exposed group depended on a cumulative exposure index ($p \leq 0.10$). Because of the administration of a chelating agent, which resulted in increased urinary mercury elimination, this study is not comparable with the other studies and is thus not suitable for the derivation of a BAT value.

Urban et al. (1999) compared visual evoked potentials and nerve conduction measurements between different groups of mercury-exposed and control subjects. She investigated 36 dentists (see above) as well as 36 chloralkali workers with current levels of 129 µg Hg/24 h, 77 workers employed in the liquefaction of mercury were showing current exposure levels of 840 µg Hg/24 h and 46 control subjects showing 0.8 µg Hg/ 24 h. In all exposed groups, a change in amplitude in the visual evoked potentials versus the control group could be identified although, on the other hand, no differences between the groups could be demonstrated. In addition to this, latent times revealed a dose-effect correlation with the quantity of flushed out mercury, which can be taken as an indicator of mercury exposure in the past. Since this dose-effect correlation could only partly be confirmed, and due to the relatively high mercury exposure of industrial workers, this investigation cannot be used for establishing the BAT value.

Investigations in former industrial workers no longer active in industry

The possible reversibility of the functional restrictions described can be discussed using studies in which formerly exposed subjects were investigated (Frumkin et al. 2001a; Kishi et al. 1994; Letz et al. 2000; Mathiesen et al. 1999). These studies present results from subjects whose current mercury exposure at the time point of investigation corresponded to that in non-exposed subjects which had, however, been considerably higher in former years.

Thus, Frumkin et al. (2001a) investigated 147 former alkali chloride workers employed between 1956 and 1994 who had no longer been exposed between 0 and 35 years (5.7 years on average). A total of 78 mercury measurements conducted between 1988 and 1991 yielded an average of 72.1 µg Hg/l urine within a range from 13.0 to 172.7 µg Hg/l urine. The current concentrations of the workers were scarcely different at 3.42 ± 2.54 µg Hg/l from those of the 132 control subjects at 3.12 ± 2.48 µg Hg/l. In the former workers, in the group comparison, all of the self-reported (subjective) symptoms were significantly increased. Also, on investigation of sensitivity to vibration, tremor, motor (response) rapidity, motor coordination and memory functions, significantly less favourable results were found in the exposed subjects. On the other hand, for the conduction velocity in the nerves of the fibular muscle (musculus peroneus), a significantly better value was obtained in the group of exposed subjects. On analysis of the relationships between exposure and effect, the nerve conduction velocities were correlated with the cumulative exposure level, motor coordination with the mean exposure, and reduced sensory nerve conduction velocities as well as verbal performances with exposure peaks. Nevertheless, a large number of relationships were found in the unexpected direction. As one possible cause for the absence of unequivocal associations, the authors discussed the study having too little "power", as only a small number of workers (4) belonged to the highest exposure category. When one takes the

fact into account that the exposure was on average 5.7 years before, the clearly changed symptoms and performances in the group comparison speak in favour of the fact that long-term mercury-conditioned effects are involved.

Mathiesen et al. (1999) investigated former alkali chloride workers whose exposure had, on average, taken place 12.7 ± 11.7 years previously. The earlier exposure to mercury was cited to be 539 ± 466 nmol Hg/l urine and year (108 ± 93 µg Hg/l urine). Average current urine mercury concentrations were in the range of background levels. In the group comparison (attentiveness/concentration, motor functions, memory), both neuropsychological changes as well as dose/effect relationships were shown for cumulative mercury exposures (memory, motor functions).

Kishi et al. (1994; see BAT documentation 1997) investigated workers whose exposure to mercury had been about 18 years previously. Some of the workers had suffered from intoxications and, at the time, showed concentrations of 500 to 2000 µg Hg/l urine. Although the acute poisoning symptoms had improved in the course of time, a comparison with suitable control subjects still manifested restrictions in attentiveness/concentration, motor functions, perception and constructive performance parameters. Exposure/effect relationships were found in the context of motor coordination, motor rapidity and perception.

More than 30 years after termination of the corresponding exposure periods Letz et al. (2000) were able to demonstrate relationships between former exposure levels of up to 635 µg Hg/l urine and nerve conduction velocity, tremor, and motor performance in 104 former workers. A particularly close association was found on examining the cumulative levels.

The findings of the four studies just cited show that, taking possible influencing factors due to age into account, functional restrictions produced by earlier exposures are not fully reversible even decades after termination of the exposure period.

By contrast, in the investigation performed by Cavalleri and Gobba (1998), a worsening in colour discrimination in 21 workers with mean levels of 115 µg Hg/g creatinine (138 µg Hg/l urine) in the subsequent year, was found to be fully reversible when the mean concentrations had decreased to 10 µg Hg/g creatinine (12 µg Hg/l urine).

Longitudinal studies

In comparison with cross sectional studies, longitudinal studies possess a greater epidemiological significance. For this reason, the results of two longitudinal studies, the contents of which had already been included in the former BAT value documentation, are here once more summarized.

In a comparison with control subjects, Günther et al. (1996) found significant correlations between symptoms, personality traits, attentiveness, memory and motor performance and mercury exposure level in 50 workers in a chloralkali electrolysis plant. They were subjected to four periods of investigations over the course of 7 years and controlled for relevant confounders. The urinary concentrations were in the range of 21 to 152 µg Hg/l. An increase in psychomotor disturbances was reported in workers with urinary concentrations of 50 to 150 µg Hg/l; a dose-effect correlation, however, could not be demonstrated.

Over a period of 2 years, Dietz et al. (1997) investigated 16 renovation workers a total of four times applying a neuropsychological test battery. Among those with a mean urinary level of 21.5 µg Hg/l (range 1.1–80 µg Hg/l), noticeable findings indicating

effects on the peripheral or central nervous system could only be identified in individual cases. However, no causal relationship with the internal mercury exposure could be shown. No control group was examined.

Meta-analytical assessment of studies

A meta-analysis (Meyer-Baron et al. 2002) on results from 12 articles published between 1980 and 1999 summarizes the results of psychological performance tests. Its aim was to evaluate the efficacy of the test ratings determined via at least three independent studies with identical test methods. In 9 parameters of test performances included from 6 different tests, significant effect sizes of mercury exposure were established. The results of investigations on 686 exposed and 579 control subjects were included. On examining the significant results of the meta-analyses for test performances, it was found that the mean exposures of those groups showing corresponding significant effect sizes were between 18 µg Hg/l (tests for attention) and 34 µg Hg/l (tests for visual memory and fine motor coordination). Between these values, 6 further, repeated tests (also including other psychomotor tests) were found which show agreement in their significant differences between exposed and control subjects. These results are usable as information on a lowest observed adverse effect level (LOAEL) between 18 and 34 µg Hg/l urine on account of their at least threefold reproducible demonstration of effects.

The fact that, in this meta-analysis, studies were also included, in which the mercury levels were markedly higher (e.g. studies on industrial workers such as by Kishi et al. 1994; Mathiesen et al. 1999) or possibly higher (e.g. studies on dentists as by Ngim et al. 1992) at former points in time, is to be noted here. The meta-analysis took into account mercury concentrations at the time point of investigation. In order to counteract a possible source of error resulting from this, among others, the concentrations, of previously employed workers found in the background exposure range were not included in the calculation of the mean concentrations. An overestimation of effects which might be produced as a result of this procedure, i.e. that workers previously subjected to higher exposures but with a currently low urinary mercury concentration were included in the effect and exposure descriptions, cannot be excluded but is, however, calculable in 5 of the studies. Hence, for example, in the study by Williamson et al. (1982) past exposure of 181 µg Hg/g creatinine contrasts with the current concentration of 133 µg Hg/g creatinine, whereas these values were found to be 120 µg Hg/g versus 58 µg Hg/g in the study by Piikivi et al. (1984), 23 µg Hg/g versus 26 µg Hg/g and 111 µg Hg/g versus 122 µg Hg/g, respectively, in the study by Günther et al. (1996), and 10 µg Hg/g versus 16 µg Hg/g creatinine in the case of Ellingsen et al. (2001). The past exposure levels are thus found to be above the current levels by factors of 1.09 to 2.06. Supposing equivalence of the studies, a mean ratio of about 1.5 is calculable for the past versus the current exposure level from the selection of studies mentioned above. This estimate cannot, however, be generalized to cover all studies considered by the meta-analysis. Therefore, the mean value of the meta-analytically determined mean current exposure will be used in the summarizing evaluation.

Analysis of dose-response relationships

A summarizing analysis of the dose-response relationship of neuropsychological test results following occupational mercury exposure was carried out by Meyer-Baron et al.

(2004). It comprises the results of 18 studies dating between 1980 and 2002. Only those studies were included that presented one or more test results in each case from three functional contexts (attention, memory, psychomotor aspects). In the three functional contexts, reduced test performances were found depending on the level of exposure. Thereby a differential effect of mercury is recognizable. The strongest correlation with urinary mercury concentrations was found for motor performance; a significant, though weaker, correlation for memory, while the exposure correlation with attention functions did not achieve statistical significance.

The question of an adversity of the changes described

If the group differences described are to be classified as effects adverse to health, i.e. as no longer tolerable, will be discussed in the following.

According to the criteria for assessing results of neurobehavioural toxicology studies (DFG 1997), the adversity of a neurotoxicological finding is confirmed in cases where the extent (proven in independently determined variables), the number (repeatedly proven) and the type (proven in different classes of methods) of the effects described in individual studies argue in favour of this. These criteria are fulfilled through the results of the meta-analysis. The required concordance of effects is fulfilled because corresponding effects could be demonstrated via varying measurement methods and in studies independent of each other. The irreversibility of effects, a further criterion, was demonstrated in four studies testing psychomotoric functions (especially motor performance and memory function; Frumkin et al. 2001a; Kishi et al. 1994; Letz et al. 2000; Mathiesen et al. 1999), however for past exposures of more than 100 µg Hg/l and up to 2000 µg Hg/l urine. In addition, the meta-analysis was able to demonstrate that the effect sizes for workers previously subjected to high exposures are not significantly different to the effect sizes in workers with current mercury concentrations between 20 and 30 µg Hg/g creatinine on average. Analysis of the exposure-effect relationships also confirmed that the effects in workers with a currently low exposure are comparable with those of workers formerly highly exposed, but followed by a longer period of no exposure. These results also argue against a complete reversibility of mercury effects on mental performance parameters. On the other hand, one study exists which indicates a reversibility, however, relating to measurements of colour discrimination only (Cavalleri and Gobba 1998).

A further route of access as regards adversity considerations is found in the analogy to age-related changes in test performance as described by Seeber et al. (2002) in the case of lead. Here, the analogy is first discussed using as example a test on memory span in subjects exposed to mercury. The meta-analytically found result giving an effect size $D^{W+} = -0.40$ in the Digit Span test (repeating numbers; functions of attention; Meyer-Baron et al. 2002) reflects a defined score difference between exposed and control subjects. This score difference corresponds to a difference of 10 years lower than that found for standard age levels in the test procedure. In other words, those subjects exposed to mean mercury concentrations of 26 µg Hg/l urine, according to the eight meta-analytically evaluated studies, show performances not corresponding with their age group. For example, an exposed person aged 45 years shows a performance corresponding to a person aged 55 years in the standard random sample (Tewes 1991). A further example: the significant effect size $D^{W+} = -0.40$ in the Benton Visual Retention test (memory function; Meyer-Baron et al. 2002) corresponds to a mean difference of

0.6 correct responses between exposed and control subjects. This value exceeds – at normal intelligence – the difference value for age groups 10 years apart from each other (Benton 1994). In four studies, an average exposure level of 26 µg Hg/l urine has been determined for this decrease in function.

A further analogy in considering adversity can be obtained from the experience gained with the concomitant effects of alcohol. At 0.3 ‰ blood alcohol (after about 500 ml beer containing 5 % alcohol), reaction times are slowed down by at least 5 % as reported (Fuchs and Resch 1996). The effect size of 0.4 in the Digit Span test cited above corresponds to a reaction time slowed down by about 5 %, and the reduced effect size of 0.4 in the Benton Visual Retention test to a reaction time slowed down by about 7 %.

Summary assessment of data on neurotoxicity

Meta-analyses investigating cross-sectional neuropsychological studies following mercury exposure have shown that, at mean current exposures between 18 and 34 µg Hg/l urine, statistically significant reductions in mental function are demonstrable compared with control subjects (Meyer-Baron et al. 2002). A dose-effect relationship has been confirmed in tests measuring the areas of motor and memory functions (Meyer-Baron et al. 2004). As regards the exposures determined, one criticism is to be raised, i.e. that, in at least some of the studies, there are indications of higher exposures in the past. The importance of these has been shown in studies in which changes in cognitive and psychomotor functions are interpreted as not being the result of current, but of past exposure (Frumkin et al. 2001a; Kishi et al. 1994; Letz et al. 2000; Mathiesen et al. 1999). No statements on the clinical relevance of the findings obtained are found in the studies mentioned.

In revising the BAT value, it is not possible to include some of the cross-sectional studies on the neurophysiological effects of mercury in industrial workers due to exposures in part above 100 µg Hg/l urine (Urban et al. 1999, 2003a), due to the questionable clinical relevance of the findings (Urban et al. 2003b) and due to the questionable clinical relevance of the findings where the former level of exposure is unclear (Lucchini et al. 2003). Nevertheless, one study is available in which workers were exposed to relatively low mercury levels over decades (Ellingsen et al. 2001). No relevant clinical changes were found in these workers at average mercury concentrations of 19 µg Hg/l urine (maximum 42 µg Hg/l) over the preceding years. A longitudinal study was able to show that psychomotor disturbances are increasingly observed in the range of 50 to 150 µg Hg/l urine (Günther et al. 1996, see BAT documentation 1997); in another longitudinal study, no indications of mercury-related psychomotor disturbances were obtained at mercury concentrations up to 80 µg Hg/l urine (Dietz et al. 1997, see BAT Documentation 1997). The data thus indicate that no clinically relevant neurotoxicological effects occur at maximum mercury concentrations of 30 µg Hg/l urine.

10.2.3 Other endpoints

Immunological effects

Experiments with rodents and in vitro investigations show that mercury compounds can have an immunomodulating activity. Thus, for example, mercury chloride and

methylmercury inhibit most lymphocyte functions in animals and humans in vitro, such as proliferation, expression of cell activation markers on cell surfaces and cytokine production. These cells exhibit a greater sensitivity to methylmercury than to mercury chloride. Repeated administration of mercury chloride to rats, mice and rabbits can induce autoimmune responses and nephropathy. In contrast, however, Lewis rats injected with mercury chloride showed immunosuppression in place of autoimmune response (Moszczyński 1997, 1999). The changes are subject to control by a number of genes, and the formation of autoantibodies is controlled by MHC (see review article by Pollard and Hultman 1997).

As with the investigations in animals, more recent findings in workers yield results which are not consistent. Some of the studies indicate immunosuppressive, other studies immunostimulatory effects (Moszczyński 1997, 1999). The investigations on immunological changes published since these reviews (Barregård et al. 1997; Dantas and Queiroz 1997; Park et al. 2000; Queiroz and Dantas 1997a, b; Soleo et al. 1997, 2002; Vimercati et al. 2001) have also yielded inconsistent results (see Table 3). Furthermore, the extent of findings observed is small, and their clinical relevance is questionable. It is also not possible to exclude that in the (slight) changes observed other factors play a role, such as methylmercury taken up with the diet or other factors. The available investigations on immunological changes in workers exposed to mercury are, therefore, not suitable for deriving a BAT value.

Thyroid function

A group of 47 chloralkali workers with current levels of 5.9 nmol Hg/mmol creatinine (12.6 µg Hg/l urine) (Ellingsen et al. 2000b, Table 4), already characterized above (see Ellingsen et al. 2000a, 2001), was divided into groups with low, medium and high exposure levels as regards the level of cumulative mercury exposure. In the high exposure group (current value 10.0 nmol Hg/mmol creatinine, corresponding to a concentration of 21.3 µg Hg/l urine), the reverse T_3 concentration as well as the ratio between free T_4 and free T_3 was increased; this especially applied to workers having low iodine concentrations in urine. The authors concluded that, particularly in the case of chloralkali workers, low urinary iodine concentrations are a risk factor for disturbances in thyroid function. In spite of this, free T_3 or TSH values were unchanged. There was evidence of reduced TNF-α concentrations in the high exposure group, which the authors attributed to the increased serum T_3 level, in order to maintain a normal thyroid function. As free T_3 and TSH were unchanged, these findings were not considered to be relevant in establishing a BAT value.

Atherosclerosis

A study by Salonen et al. (2000) shows an accelerated progression of carotid atherosclerosis when accumulation of mercury in the hair has reached more than 2.81 µg Hg/g. This investigation is not suitable to derive a BAT value, as the mercury concentration in urine was not determined.

Enzyme activities in blood

In workers with a exposure of 77.44 ± 48.15 µg Hg/l, Zabinski et al. (2000) demonstrated changes in haematological parameters and in erythrocytic enzymes.

Queiroz et al. (1998) showed, in workers exposed to mercury with 18.5 ± 8.8 (range 4.7–37.5) µg Hg/g creatinine, corresponding to 22 ± 11 (range 5.6–45) µg Hg/l urine, reduced GSH and increased catalase activity; no correlation to the extent and duration of mercury exposure was found.

Micronuclei

Increased micronucleus rates were described by Queiroz et al. (1999) in 15 workers from a mercury-producing plant having 19.3 ± 13 µg Hg/g creatinine (about 23.2 ± 16 µg Hg/l urine). However, no correlation was found between the micronucleus rate and the duration of exposure, or the urinary mercury concentration. As control, 15 blood samples were used from a blood bank comprising subjects of the same age. Because of the inadequate characterization of the controls (absence of socioeconomic factors, smoking habits, mercury determination method), it is not possible to evaluate the significance of these results.

Increased rates of micronuclei, sister chromatid exchanges and HPRT mutations were recorded in the blood cells of 30 chloralkali workers with mean urinary concentrations of 215 ± 36 µg Hg/g creatinine (about 258 ± 43 µg Hg/l urine), compared with 30 control subjects of the same age and having the same socioeconomic standards (Shamy et al. 1995).

Mortality

Boffetta et al. (2001) investigated mortality data in a group of 6784 males and 265 females employed in mercury mines and mills in four countries (Italy, Spain, Slovenia and the Ukraine) between 1900 and 1990, and compared them with national reference data. Though the mercury exposure levels varied greatly, they were generally very high. Thus, workers in Spanish mines showed urinary concentrations of up to 1500 µg Hg/l between 1930 to 1960, from 1985 they were between 100 to 300 µg Hg/l in Spain and Slovenia. In mills, exposure levels of 500 to 600 µg Hg/l (Italy, Slovenia, Ukraine) or 300 µg Hg/l (Spain) were cited up to 1960. From 1980 on, the exposure levels dropped to 300 µg Hg/l, or to 100 to 150 µg Hg/l respectively. A cumulative exposure index was drawn up for every worker. Significantly increased, standardized mortality rates (SMR) were found for all cases of death (SMR 1.08, 95 % confidence interval (CI) 1.04–1.12), hypertension (SMR 1.46, 95 % CI 1.08–1.93) and “heart diseases other than ischaemic” (SMR 1.36, 95 % CI 1.20–1.53). The highest SMR was found for nephritis and nephrosis (SMR 1.55, 95 % CI 1.13–2.06), which even reached 1.71 (95 % CI 1.16–2.43) for workers in the mercury mines. The relative mortality risk in the case of nephritis or nephrosis correlated with the duration of employment but not with the cumulative exposure to mercury.

10.3 Selection of the indicators

For biomonitoring a mercury exposure, a number of parameters can be taken into account, such as blood, urine, hair, fingernails, exhaled air and saliva. From the standpoint of occupational medicine, however, only the determination of mercury in blood and urine is relevant (see BAT documentation 1997).

Blood

The concentration of mercury in blood is, in the first place, influenced by the current mercury exposure as well as by the intake of organic mercury compounds (for example methylmercury from fish) (see BAT documentation 1997). This becomes particularly noticeable in an evaluation of different studies by Brune et al. (1991). Here, 98 publications dealing with normal mercury levels in blood were evaluated. The group of subjects not consuming fish showed a mean concentration of 2 µg Hg/l, in the group eating more than four fish meals per week the mean value reached 44 µg Hg/l. In more recent investigations as well, the significant influence of taking fish meals on mercury concentrations in blood was confirmed (e.g. Langworth et al. 1997). The parameter "mercury in whole blood" is hence not specific enough to indicate an occupational exposure to inorganic and metallic mercury. From the correlation between blood mercury and urinary mercury taken as basis for the last BAT documentation, a BAT value of 30 µg Hg/l urine corresponds to a blood level of about 8 µg Hg/l. This whole blood mercury concentration is also attained by subjects with high fish consumption.

Urine

There is evidence that the elimination of mercury in the urine correlates with the mercury content in the kidneys. Assuming this, therefore, and after long-term exposure, the urine mercury concentration seems to be an indicator especially for chronic mercury exposure (see BAT documentation 1997). More recent investigations confirm this assumption.

In determining mercury exposure levels, there is also the possibility of administering chelating agents such as DMSA (dimercaptosuccinic acid) to the subjects investigated. By this means, higher mercury concentrations are measured in urine (e.g. Frumkin et al. 2001b). This method is not considered in deriving a BAT value.

10.4 Background exposure

In an environmental survey conducted in 1998, the 95th percentile of the mercury exposure found in the German population aged 18 to 69 years (n = 4741) was 3.3 µg Hg/l urine. Subjects without amalgam fillings (n = 1560) were found to have a 95th percentile of their mercury exposure at 1.1 µg Hg/l urine (Becker et al. 2003; HBM 2003).

10.5 Evaluation of the BAT values

Mercury in blood

The parameter "mercury in blood" is considerably influenced by the intake of organic mercury compounds (methylmercury) in the form of fish meals (Brune et al. 1991). Starting from the previously assumed correlation between blood and urinary mercury concentrations, the concentrations of 30 µg Hg/l urine in subjects without significant fish consumption would result in concentrations of about 8 µg Hg/l blood (see BAT documentation 1997). This value for mercury in blood is reached and even exceeded by

subjects having high fish consumption. The parameter is therefore not specific enough to determine occupational exposures to metallic and inorganic mercury.

The parameter "mercury in blood" is therefore not used further.

Mercury in urine

The data presented above both on neurotoxicity and on nephrotoxicity indicate that – taking the 95th percentile into account – no clinically relevant neurotoxic changes or relevant mercury-related nephrotoxic effects are to be expected at a concentration of 30 µg Hg/l urine.

The BAT value is therefore set at

30 µg Hg/l urine.

No fixed time for sampling.

10.6 Interpretation of the data investigated

In the Federal Republic of Germany, preventive occupational medical examinations of subjects exposed to mercury are carried out in accordance with principle G9 of the trade association, in which time intervals are laid down for follow-up investigations. More frequent examinations are recommended in cases where findings are in the limit value range.

There is no fixed sampling time for blood and urine specimen to analyse mercury. However, for reasons of standardization, the specimens should be sampled at the end of a current working week.

It applies to both blood and urine that sampling must be properly performed. Attention must also be paid to selecting adequate containers for sending the material in, the preserving agents used, and correct storage conditions. On the one hand, contamination can occur due to contaminated clothing, sampling equipment or transport containers. On the other hand, losses of mercury due to absorption into container walls, reduction and evaporation, as well as due to a bacteriologically or chemically induced precipitation have been observed. Such losses can be avoided by the addition of oxidants, such as nitric acid to the urine, and storage of the samples in a deep freezing unit. Prior to analysis, the urine sample must be well shaken, as mercury can be bound up in the urinary sediment.

In cases of exposure to metallic mercury and its inorganic compounds, measurement of the urinary mercury concentration is to be preferred.

The BAT value relates to normally concentrated urine, in which the creatinine content ought to be in the range of 0.5 to 2.5 g/l. Where the urine is highly concentrated or diluted, the physician involved will have to decide whether the BAT value can be considered as being adhered to or is exceeded. As a rule, where urine samples are outside the limits quoted above, a repetition of the measurement in normally hydrated volunteers is recommended.

A correction for creatinine of the volume-related mercury measurement is at present not required, as distortions in measurement results can be expected. This is firstly due to the fact that there is, as yet, no experimentally confirmed evidence that the mode of renal excretion is equivalent for mercury and creatinine. Secondly, the analytical

determination of a creatinine concentration in urine is accompanied by measurement inaccuracies which cannot be disregarded, a fact reflected in interlaboratory tests on urine creatinine analysis. Here, it was only possible to obtain 60 % to 70 % of the values from participating laboratories within the defined tolerance range.

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Table 1. Nephrotoxic effects after occupational exposure to inorganic mercury

Author	Number, collective, exposure duration		Current Hg concentration in urine (Hg-U)	Findings
Mortada et al. 2002	49	**healthy subjects with amalgam** fillings, 31.0 years old, non-smokers	1.8 ± 0.5 µg/g creatinine (**2.2 ± 0.6 µg/l**)	**NAG**: 3.0 ± 1.2 U/g creatinine (+ amalgam) 2.2 ± 0.5 U/g creatinine (– amalgam) **γ-GT**: 32.9 ± 9.9 U/g creatinine (+ amalgam) 24.0 ± 7.0 U/g creatinine (– amalgam) **albumin**: 6.7 ± 1.7 mg/g creatinine (+ amalgam) 3.2 ± 2.2 mg/g creatinine (– amalgam)
	52	**healthy subjects without amalgam** fillings, 31.8 years old, non-smokers	0.5 ± 0.2 µg/g creatinine (**0.6 ± 0.3 µg/l**)	
Rojas et al. 2000	22	**dentists**, 43.5 years old exposed for 16.5 ± 9.1 years	22.4 ± 6.4 µg/g creatinine (**26.9 ± 7.7 µg/l**)	**NAG**: **no statistically significant difference**: 2.9 ± 3.0 (0–32.5) U/l (dentists) 5.2 ± 8.1 U/l (assistants)
	15	**assistants**, 43.5 years old, exposed for 14.7 ± 6.2 years	22.2 ± 6.1 µg/g creatinine (**26.6 ± 7.3 µg/l**)	
Alinovi et al. 2002	122	**workers**, 40.2 years old, exposure duration not specified	8.1 ± 1.9 (2.3–35.0) µg/g creatinine [**9.7 ± 2.3 (2.8–42) µg/l**]	**no significant effect on renal parameters** (NAG, albumin, β_2M, RBP, 3 brush-border antigens, fibronectin)
	197	**controls**, 38.7 years old	1.1 ± 2.6 (0.1–5.9) µg/g creatinine [**1.3 ± 3.1 (0.1–7.1) µg/l**]	
Camerino et al. 2002	38	**workers** (chloralkali), 38.6 years old, exposed for 13 ± 10.5 years	11.9 ± 8.1 (2–35) µg/g creatinine [**14.3 ± 9.7 (2.4–42) µg/l**]	**no significant effect on renal parameters** (NAG, albumin, β_2M, RBP, 3 different brush-border antigens, fibronectin)
	34	**controls**, 50.6 years old	4.1 ± 5.9 (1–33) µg/g creatinine [**4.9 ± 7.1 (1.2–40) µg/l**]	

Table 1. (continued)

Author	Number, collective, exposure duration		Current Hg concentration in urine (Hg-U)	Findings
Ellingsen et al. 2000a	47	**workers** (chloralkali), 42.0 years old, exposed for 13.3 (2.8–34.5) years, 53 % smokers, 3.9 l ethanol/a	5.9 (1.1–16.8) nmol/mmol creatinine [**12.5 (2.3–35.7) µg/l**]	**NAG**: statistically significant difference: 0.18 ± 0.09 U/mmol creatinine (exposed) 0.14 ± 0.10 U/mmol creatinine (controls) **other renal parameters** in urine (e.g.: albumin, β_2M, IAP, GAG, Kal) and serum **not changed**; however, after stepwise multiple linear regression significant changes in autoantibodies against myeloperoxidase and proteinase 3
	47	**controls**, 41.9 years old, 34 % smokers, 3.9 l ethanol/a	1.3 (0.2–5.0) nmol/mmol creatinine [**2.8 (0.4–10.6) µg/l**]	
El-Safty et al. 2003	27	**workers** (**NS**), 32.9 ± 5.1 years old, exposed for 7.89 ± 2.0 years	25.6 ± 19.3 µg/g creatinine (**30.7 ± 23.2 µg/l**)	**non-smokers (NS)** **total protein**: 152 ± 5.44 mg/g creatinine (> 11 a exp.) 131 ± 16.0 mg/g creatinine (< 10 a exp.) 75.3 ± 15.3 mg/g creatinine (controls) **RBP**: 22.1 ± 3.8 µg/g creatinine (> 11 a exp.) 14.4 ± 2.6 µg/g creatinine (< 10 a exp.) 6.9 ± 2.5 µg/g creatinine (controls) **LAP:** 18.7 ± 5.3 U/g creatinine (>11 a exp.) 13.0 ± 2.4 U/g creatinine (<10 a exp.) 6.6 ± 1.8 U/g creatinine (controls) **GST**: 8.8 ± 1.4 µmol/min/mg creatinine (> 11 a exp.) 7.8 ± 1.4 µmol/min/mg creatinine (< 10 a exp.) – (controls) **NAG**: 19.1 ± 4.1 nmol/mg creatinine (> 11 a exp.) 11.8 ± 1.9 nmol/mg creatinine (< 10 a exp.) 6.9 ± 2.1 nmol/mg creatinine **data of smokers (S)** see publication
	20	**workers (NS),** 39.5 ± 8.5 years old, exposed for 17.85 ± 8.46 years	21.4 ± 15.9 µg/g creatinine (**25.7 ± 19.1 µg/l**)	
	36	**controls (NS),** 35.6 ± 9.5 years old	0.57 ± 0.42 µg/g creatinine (**0.8 ± 0.5 µg/l**)	
	34	**workers (S)** 33.6 ± 5.6 years old, exposed for 8.79 ± 1.97 years	17.3 ± 5.22 µg/g creatinine (**20.7 ± 6.4 µg/l**)	
	31	**workers (S)** 42.1 ± 8.3 years old, exposed for 19.2 ± 7.56 years	28.2 ± 21.4 µg/g creatinine (**33.8 ± 25.7 µg/l**)	
	51	**controls** (S), 44.0 ± 10.8 years old	0.62 ± 0.44 µg/g creatinine (**0.7 ± 0.5 µg/l**)	

Table 1. (continued)

Author	Number, collective, exposure duration		Current Hg concentration in urine (Hg-U)	Findings
Cárdenas et al. 1993 (see also BAT Documentation 1997)	44	**workers** (chloralkali), 38 ± 9.8 years old, exposed for 11.2 ± 6.8 years, 22.7 % smokers, 75 % alcohol drinkers	**31.9 (3.7–169) µg/l**	**NAG**: not changed **β_2M**: 48 (4–277) µg/l (exp.) 77 (24–232) µg/l (controls) **THG**: 27.1 (11.4–72.5) mg/l (exp.) 16.1 (2.9–65.3) mg/l (controls) **BB_{50}**: 12.5 (1.8–58.3) U/l (exp.) 9.2 (2.0–32.0) U/l (controls) **BBA**: 7.9 (1.9–35.7) U/l (exp.) 5.7 (1.1–22.7) U/l (controls) **HF5**: 9.0 (2.4–38.5) U/l (exp.) 6.4 (1.4–37.8) U/l (controls) **IAP**: 1.02 (0.22–8.26) U/l (exp.) 0.67 (0.13–3.52) U/l (controls) **PGE_2**: 159 (49–411) ng/l (exp.) 244 (106–569) ng/l (controls) **$PGF_{2\alpha}$**: 337 (19–1305) ng/l (exp.) 531 (127–1685) ng/l (controls) **TXB_2**: 66 (32–177) ng/l (exp.) 98 (31–175) ng/l (controls) **GAG**: 46.5 (16.2–92) mg/l (exp.) 55 (32–78) mg/l (controls) **serum creatinine (blood)**: 10.1 ± 1.1 mg/l (exp.) 10.8 ± 1.1 mg/l (controls)
	49	**controls** 29.8 ± 9.5 years old, 34.7 % smokers, 92 % alcohol drinkers	**2.3 (0.5–10.8) µg/l**	
Price et al. 1996 (with data from Cárdenas et al. 1993)	18 + 45	**workers**, exposed for 11 (1.5–25) years; smoker status like controls; 75% alcohol drinkers	< 5 µg/g creatinine **(< 6 µg/l)**; 5–50 µg/g creatinine (**6–60 µg/l**); > 50 µg/g creatinine (**> 60 µg/l**)	**< 6 µg/l**: no effects on renal parameters **6–60 µg/l**: most renal parameters in urine slightly increased; significantly increased: PGE_2, $PGF_{2\alpha}$, TXB_2, **> 60 µg/l**: many renal parameters in urine increased; significantly increased: BB_{50}, BBA, HF5, IAP, PGE_2, $PGF_{2\alpha}$, TXB_2, Kal, GAG
	23 + 48	**controls**, 92 % alcohol drinkers	not specified	

Table 1. (continued)

Author	Number, collective, exposure duration		Current Hg concentration in urine (Hg-U)	Findings
Abdennour et al. 2002	61	**controls ("Site 1")**, 35.5 ± 8.9 years old	2.1 ± 1.4 µg/g creatinine **(2.5 ± 1.7 µg/l)**	**proteinuria (> 0.3 g/l)**: 4.9 % of workers ("Site 1", controls) 14.6 % of workers ("Site 2") 39 % of workers ("Site 3") **pH of the urine < 6.5**: 24 % of workers ("Site 1", controls) 53 % of workers ("Site 2") 64 % of workers ("Site 3")
	82	**workers ("Site 2")**, 42.8 ± 5.4 years old, exposed for 12.8 ± 4 years	29.3 ± 23.2 µg/g creatinine (**35.2 ± 27.8 µg/l**)	
	64	**workers ("Site 3")**, 38.7 ± 7.0 years old, exposed for 11.6 ± 5 years	138.6 ± 80.9 µg/g creatinine (**166 ± 97.1 µg/l**)	

Abbreviations: NAG: N-acetyl-β,D-glucosaminidase; β_2M: β_2-microglobulin; γ-GT: γ-glutamyl transpeptidase; BB_{50} and BBA: brush-border antigens; GAG: glycosaminoglycanes; GST: glutathione transferase; HF5: brush-border antigen; IAP: intestinal alkaline phosphatase; Kal: kallikrein; LAP: leucine aminopeptidase; PGE_2,: prostaglandin E_2; $PGF_{2\alpha}$: prostaglandin $F_{2\alpha}$; RBP: retinol-binding protein; THP: Tamm-Horsfall glycoprotein; TXB_2: thromboxane B_2; exp.: exposed

Table 2. Neurological and neuropsychological effects after occupational exposure to inorganic mercury (arranged according to increasing mercury exposure)

Author	Number, collective, exposure duration		Hg concentration in urine (Hg-U)	Findings
Echeverria et al. 1998	48	**dental medical personnel**; on average 49 years old, exposure duration not specified	current Hg-U: **0.89 ± 0.51 µg/l** (dentists), **1.07 ± 0.93 µg/l** (assistants)	questionnaire symptoms, questionnaire mood, 10 neuropsychological tests; dose-response relationship: questionnaire mood (sum of all mood scales, tension, anger, fatigue, confusion, depression), 2/5 motor function tests, 3/4 attention tests, 1/1 memory test
Aydin et al. 2003	43	**dental medical personnel,** median age: 32 years; exposure duration not specified	current Hg-U: 1.17 (0.01–3.39) nmol/mmol creatinine [**2.5 (0.02–7.2) µg/l**]	questionnaire symptoms, personality questionnaire, 4 neuropsychological Tests; unfavourable values at group comparison: symptoms; reduced performance at group comparison: 1/3 memory tests; dose-response relationship: 1/3 memory tests; symptoms (anger, psychosis)
	43	**controls**, median age: 31 years (comparable or older, education, alcohol, fish consumption, smoking)	current Hg-U: 0.64 (0.01–2.76) nmol/mmol creatinine [**1.4 (0.02–5.9) µg/l**]	
Ritchie et al. 2002	162	**dentists,** 39.3 ± 9.7 years old, exposed for 15.6 ± 9.5 years	current Hg-U: 2.58 ± 2.76 nmol/mmol creatinine (**about 5.5 ± 5.9 µg/l**)	questionnaire diseases, questionnaire symptoms, 6 neuropsychological tests; unfavourable values at group comparison: diseases (kidneys), symptoms (retentivity); reduced performance at group comparison: 1/3 attention tests, 1/3 memory tests; dose-response relationship: 1/3 memory tests
	163	**controls**, 32.1 ± 9.7 years old (**significantly younger than dentists**)	current Hg-U: 0.67 ± 0.68 nmol/mmol creatinine **(about 1.4 ± 1.4 µg/l)**	

Table 2. (continued)

Author	Number, collective, exposure duration	Hg concentration in urine (Hg-U)	Findings
Langworth et al. 1997	44 **dental medical personnel**; median age: 43 years; exposed for 20 years (8–35 years)	current Hg-U: 3.0 ± 2.3 nmol/mmol creatinine (**6.4 ± 4.9 µg/l**)	questionnaire symptoms, questionnaire complaints, personality questionnaire, questionnaire mood; unfavourable values at group comparison: questionnaire complaints, questionnaire mood (anger); no dose-response relationship
	44 **controls,** (of comparable sex, age, and education) median age: 45 years	current Hg-U: 2.3 ± 1.6 nmol/mmol creatinine **(4.9 ± 3.4 µg/l)**	
Urban et al. 1999	36 **dentists**, 41 years old, exposed for 14 years	current Hg-U: **13.2** µg/24 h (≈ **µg/l**)	EEG measurement; reduced performance at individual and group comparison: visual evoked potential; dose-response relationship: 1/5 neurophysiological variables
	46 **controls**, 36 years old	current Hg-U: **0.8** µg/24 h (≈ **µg/l**)	
Bittner et al. 1998	230 **dentists** (from 6 studies), 50 ± 12 years old, exposure duration not specified	current Hg-U: 7 % > **55 µg/l** 93 % **< 55 µg/l**	4 neuropsychological tests, tremor measurement; dose-response relationship: 1/3 motor function tests
Ellingsen et al. 2001	47 **workers** (chloralkali), 42 (24–67) years old, 53 % smokers, exposed for 13.3 years	current Hg-U: 5.9 (1.1–16.8) nmol/mmol creatinine [**12.6 (2.3–36) µg/l**] cumulative Hg-U: 123 (14.5–491) nmol/mmol creatinine [**261 (31–1044) µg/l**] mean Hg-U/year: 9.0 (4.0–19.6) nmol/mmol creatinine [**19 (8.5–42) µg/l**]	questionnaire complaints 9 neuropsychological tests; no reduced performance at group comparison; dose-response relationship (for mean Hg-U/year): 1/3 attention tests; dose-response relationship (for Hg-B): 1/3 attention tests, 1/1 memory test

Table 2. (continued)

Author	Number, collective, exposure duration		Hg concentration in urine (Hg-U)	Findings
	47	**controls**, 42 (23–64) years old (comparable or older, education, alcohol, shift work), 34 % smokers	current Hg-U: 1.3 (0.2–5.0) nmol/mmol creatinine [**2.7 (0.4–10.6) µg/l**]	
Lucchini et al. 2002, 2003	122	**workers** (chloralkali, thermometers, fluorescent lamps), 40.2 ± 10.3 years old; exposed for 14.6 ± 10.1 years	current Hg-U: mean: 10.4 ± 6.9 (0.2–35.2) µg/g creatinine [**12.5 ± 8.3 (0.2–42.2) µg/l**] 95th percentile: 23.5 µg/g creatinine [**28.2 µg/l**]	questionnaire symptoms, 7 neuropsychological tests, tremor measurement, measurement of prolactin in serum; reduced performance at group comparison: 1/3 motor function tests; dose-response relationship (for occupational exposure): 2/3 motor function tests, prolactin concentration
	196	**controls**, 38.7 ± 11.5 years old (of comparable age, alcohol); significantly longer school education, more amalgam	mean: 1.9 ± 2.8 (0.1–33.2) µg/g creatinine **[2.3 ± 3.4 (0.1–39.8) µg/l]** 95th percentile: 5.42 µg/g creatinine **(6.5 µg/l)**	
Urban et al. 2003 b	24	**workers** (chloralkali), 42 ± 9.8 years old, significantly higher alcohol and tobacco consumption than controls, exposed for 14.7 ± 9.7 years	current Hg-U: 20.5 ± 19.3 (0.15–61.7) µg/g creatinine [**24.6 ± 23.2 (0.18–74.0) µg/l**]	colour vision; reduced performance at group comparison: colour vision; no dose-response relationship
	24	**controls**, 43 ± 11 years old	–	

Table 2. (continued)

Author	Number, collective, exposure duration		Hg concentration in urine (Hg-U)	Findings
Urban et al. 2003 a	24	**workers** (chloralkali), 42 ± 9.8 years old, exposed for 15 ± 9.7 years	current Hg-U: **64.3 ± 59.9** µg/24 h (≈ **µg/l** assuming an excretion of 1 l urine in 24 h) after administration of a chelating agent	EEG measurement; reduced performance at group comparison: reaction to light stimuli; dose-response relationship (für cumulative exposure, p ≤ 0.10): reaction to light stimuli
	24	**controls**, 36 ± 11 years old	–	
Urban et al. 1999	36	**workers** (chloralkali), 39 years old, exposed for 9 years	current Hg-U: **129** µg/24 h (≈ **µg/l**)	EEG measurement, measurement of nerve conduction velocity; reduced performance at group comparison: visual evoked potential; dose-response relationship (for excreted mercury): visual evoked potential
	77	**workers** ("Hg"), 39 years old, exposed for 9 years	current Hg-U: **840** µg/24 h (≈ **µg/l**)	
	46	**controls**, 36 years old	current Hg-U: **0.8** µg/24 h (≈ **µg/l**)	
Frumkin et al. 2001 a	147	**former workers** (chloralkali), 49.5 ± 13.0 years old, exposure duration not specified **no longer been exposed during the previous 5.7 ± 6.5 years**	current Hg-U: **3.42 ± 2.54 µg/l** Hg-U 1988–1991: **72 (13–173) µg/l**	questionnaire symptoms, 11 neuropsychological tests, colour vision, tremor measurement, body coordination, neurological investigation; reduced performance at group comparison: 1/2 memory tests, 2/2 motor function tests, tremor measurement;
	132	**controls**, 49.5 ± 13.0 years old	current Hg-U: **3.12 ± 2.48 µg/l**	reduced performance at group comparison: nerve conduction velocity, vibration sense, tremor, symptoms (dizziness, loss of balance, difficulty concentrating, confusion, memory trouble, irritability, depression, sleep disturbances, difficulty grasping), 2/2 motor function tests, 1/2 memory tests;

Table 2. (continued)

Author	Number, collective, exposure duration	Hg concentration in urine (Hg-U)	Findings
			dose-response relationship (for mean Hg-U): 1/3 motor function tests; dose-response relationship (for maximum Hg-U): nerve conduction velocity
Mathiesen et al. 1999	75 **former workers** (chloralkali), 44.7 years old, 57 % smokers, 25.3 % shift workers, exposed for 7.9 ± 6.8 years, **no longer been exposed during the previous 12.7 ± 11.7 years**	current Hg-U: 1.8 ± 1.3 nmol/mmol creatinine (**3.8 ± 2.8 µg/l**) cumulative Hg-U: 3244 ± 3178 nmol/l (**650 ± 637 µg/l**) mean Hg-U/year: 539 ± 466 nmol/l (**108 ± 93 µg/l**)	13 neuropsychological tests; reduced performance at group comparison: 1/5 attention tests, 1/5 memory tests, 1/3 motor function tests; dose-response relationship (for cumulative Hg-U): 1/5 memory tests, 1/3 motor function tests; dose-response relationship (for mean Hg-U/year): 2/5 attention tests, 2/5 memory tests, 1/3 motor function tests
	52 **controls**, 45.5 years old, (comparable or older, education, alcohol consumption), 67.9 % smokers, 42.3 % shift workers	current Hg-U: 1.2 ± 0.6 nmol/mmol creatinine (**2.6 ± 1.3 µg/l**)	
Letz et al. 2000	104 **former workers,** 70.3 ± 5.9 years old; exposure duration not specified, **no longer been exposed during the previous 30 years**	mean Hg-U/exposed quarter: **201 ± 98 (64–6956) µg/l** peak exposure: **635 ± 320 (187–1900) µg/l** cumulative Hg-U: **3362 ± 1177 (1089–6588) µg/l**	questionnaire mood, 11 neuropsychological tests, tremor measurement loss of balance, neurological investigation; reduced performance at group comparison: sensorical conspicuities, 1/8 parameters of nerve conductivity;

Table 2. (continued)

Author	Number, collective, exposure duration		Hg concentration in urine (Hg-U)	Findings
	101	**controls,** 71.1 ± 6.6 years old (comparable with regard to age, income, alcohol, BMI)	not specified	dose-response relationship (for cumulative Hg-U): 2/8 parameters of nerve conductivity, 1/3 motor function tests; dose-response relationship (during exposure): 1/8 parameters of nerve conductivity, tremor measurement
Cavalleri and Gobba 1998	21	**workers,** 26.5 ± 6.6 years old, exposed for 115.8 ± 71 months	Hg-U 1994: 115 ± 62 µg/g creatinine (**138 ± 74 µg/l**) Hg-U 1995: 10 ± 7.6 µg/g creatinine (**12 ± 9 µg/l**)	colour vision; reduced performance at group comparison 1994: colour vision; no reduced performance at group comparison 1995
	21	**controls**, 26.7 ± 6.5 years old (comparable with regard to age, smoking, alcohol)	not specified	

Table 3. Immunologic effects after occupational exposure to inorganic mercury

Author	Number, collective, exposure duration		Current Hg concentration in urine (Hg-U)	Findings
Vimercati et al. 2001	19	**workers** (fluorescent lamps), 40.3 ± 8.9 years old, 16.4 ± 8.7 working years, exposure duration not specified	**9.7 ± 5.5 µg/l**	no significant difference between exposed and controls (leukocytes, lymphocytes, monocytes); however, number of **CD13**- and **CD15 cells** and **NK cells** reduced with increasing cumulative Hg-U in exposed workers; impairment of the polymorphonuclear leukocyte chemotaxis in exposed workers
	25	**controls**, 44.3 ± 9.0 years old, 16.6 ± 7.2 working years	**2.4 ± 1.2 µg/l**	
Soleo et al. 2002	117	**workers** (fluorescent lamps), 45.6 ± 4.5 years old, exposed for 21.5 ± 1.2 years	10.4 ± 6.9 (0.2–35.2) µg/g creatinine [**12.5 ± 8.3 (0.2–42.2) µg/l**]	number of **$CD4^+$ cells** significantly ($CD8^+$ cells not significantly) increased in exposed workers, **cytokine IL-8** significantly decreased, inverse correlation between cytokines in serum and Hg-U
	172	**controls** (population), 46.7 ± 6.2 years old	2.4 ± 3.3 (0.1–33.2) µg/g creatinine [**2.9 ± 4.0 (0.1–40.0) µg/l**]	
Queiroz and Dantas 1997 a, b	33	**workers** (Hg production), on average 29 (19–46) years old, exposed for 19 (3–72) months	19.8 ± 10.3 (1.4–46.0) µg/g creatinine [**23.8 ± 12.4 (1.7–55.2) µg/l**]	**B lymphocytes**, significantly decreased; no correlation with Hg exposure or exposure duration; **T lymphocytes**: $CD4^+$ cells decreased; ratio $CD4^+/CD8^+$ significantly decreased; no correlation with Hg exposure or exposure duration
	8 and 13, resp.	**controls**, not further specified and 28 ± 7.6 years old, respectively	< 5 µg/g creatinine **(< 6 µg/l)**	
Dantas and Queiroz 1997	36	**workers** (Hg production), mean age 27 (19–46) years, exposed for 19 (3–72) months	19.4 ± 10 (1.4–46.0) µg/g creatinine [**23.3 ± 12 (1.7–55.2) µg/l**]	**IgE** increased**;** mean: 503.2 (95 % KI 7.5–2000) IU/mL (normal value up to 200 IU/mL); highly increased IgE values in some workers with "short" exposure duration (maximum 15 months); with increasing exposure decrease of IgE values; no data on a correlation between IgE values and Hg exposure
	not specified	not further specified	background exposure < 5 µg/g creatinine **(< 6 µg/l)**	

Table 3. (contributed)

Author	Number, collective, exposure duration		Current Hg concentration in urine (Hg-U)	Findings
Barregård et al. 1997	41	**workers** (chloralkali), 36 (18–61) years old, exposed for 9 (1–20) years	27 (7.8–94) µg/g creatinine [**32 (9.4–113) µg/l**]	no differences in IgE, autoantibodies or immune complexes (blood) or albumin (urine)
	41	**controls**, 36 (18–61) years old	3.4 (0.9–8.8) µg/g creatinine [**4.1 (1.1–10.1) µg/l**]	
Soleo et al. 1997	34	**workers** (fluorescent lamps), 45.6 ± 4.4 years old, exposed for 21.5 ± 1.2 years	continuously decreasing from **36.0 ± 13.3 µg/l** (1978) to **6.0 ± 2.8 µg/l** (1994)	reduced **TNF-α** associated with Hg exposure , but no dose-response relation between Hg-U and TNF-α
	35	**controls**, 46.7 ± 6.2 years old	2.6 ± 1.7 µg/l (1994)	
Park et al. 2000	20	**workers** (fluorescent lamps), 24 (21–34) years old, exposed for 31 months (4–62 months)	**44.8 ± 36.6 (1.8–163) µg/l**	number of **$CD4^+$**$CD45RA^+$-T-lymphocytes and total $CD4^+$-lymphocytes significantly decreased; number of $CD57^+CD16^+$-NK cells inversely correlated with Hg-U
	20	**controls**, (of comparable age, smoking)	not specified	

Abbreviations: CD: cluster of differentiation (cell surface antigens); Ig: immune globulin; IL: interleukin; NK cells: natural killer cells; TNF-α: tumour necrosis factor α

Table 4. Other changes after occupational exposure to inorganic mercury

Author	Number, collective, exposure duration		Hg concentration in urine (Hg-U)	Findings
Ellingsen et al. 2000 b	47	**workers** (chloralkali), 42 (24–67) years old, exposed for 13.3 (2.8–35) years	current Hg-U: 5.9 (1.1–16.8) nmol/mmol creatinine [**12.6 (2.3–36) µg/l**] mean Hg-U/year: 9.0 (4.0–19.6) nmol/mmol creatinine [**19 (8.5–42) µg/l**]	**thyroid function** **reverse** triiodothyronine **(rT_3):** 268 (161–422) pmol/l significantly increased (controls: 232 (129–352) pmol/l); after separation according to level of exposure significant difference in "high" exposure group only, current exposure 10.0 (5.8–16.8) nmol/mmol creatinine corresponding to 21.3 (12.3–36) µg/l und cumulative exposure of 12.6 (10.2–19.6) nmol/mmol creatinine and year, corresponding to 26.7 (21.7–41.7) µg/l and year
	47	**controls,** 41 (23–64) years old	1.3 (0.2–5.0) nmol/mmol creatinine [**2.8 (0.4–10.6) µg/l**]	
Zabinski et al. 2000	46	**workers,** 39 ± 10.4 years old, exposed for 14.7 ± 10.8 years	current Hg-U: **77.4 ± 48.2 µg/l**	**measurement of enzymes in erythrocytes, haematological parameters of peripheral blood** enzymes in erythrocytes: G6PD, glutathione reductase and SOD decreased, AChE inceased; haematological parameters: haematocrit and number of erythrocytes increased, MCV, MCHC, ferritin, transferritin and total Fe binding capacity decreased
	35	**controls**; 33.6 ± 9.8 years old	not further specified	
Queiroz et al. 1998	16	**workers** (Hg production), 32 (18–48) years old, exposed for 3.3 (0.5–8) years	current Hg-U: 18.5 ± 8.8 (4.7–37.5) µg/g creatinine [**22.2 ± 10.6 (5.6–45.0) µg/l**]	**antioxidative enzymes (blood):** in Hg-exposed workers GSH in erythrocytes significantly decreased, catalase significantly increased (compared with former workers and also with controls); no differences in SOD and G6PD
	11	**former workers** (with metal intoxications), 46 (42–61) years old, exposed for 4–10 years; **no longer been exposed during the previous > 6 months**	current Hg-U: 10 ± 6.7 (5.0–19.0) µg/g creatinine [**12 ± 8.0 (6–22.8) µg/l**]	
	11	**controls**, (with comparable age, race)	background exposure < 5 µg/g creatinine (< 6 µg/l)	

Table 4. (continued)

Author	Number, collective, exposure duration		Hg concentration in urine (Hg-U)	Findings
Queiroz et al. 1999	15	**workers** (Hg production), 39.5 (27–53) years old, exposed for 12 (5–28) years	current Hg-U: 19.3 ± 13.0 (7.5–48.9) µg/g creatinine [**23.2 ± 15.6 (0.0–58.7) µg/l**]	**micronucleus** rate (blood cells) significantly increased at about 1–7 % (controls 0–1 %) but no correlation between micronuclei and age, exposure duration and Hg-U
	15	**blood samples from blood bank** (from subjects of comparable age without Hg exposure)	background exposure < 5 µg/g creatinine (< 6 µg/l)	
Shamy et al. 1995	30	**workers** (chloralkali), 35 ± 0.3 years old; exposed for 10.0 ± 0.3 years	current Hg-U: 215 ± 36.1 µg/g creatinine (**258 ± 43.3 µg/l**)	significantly increased rates of **micronuclei** in blood cells (32.0 ± 1.7/1000; controls 14.0 ± 2.4/1000), **SCE** (7.3 ± 0.2; controls 4.6 ± 0.6) and **HPRT mutations** (0.94 ± 0.01; controls 0.83 ± 0.07)
	30	**controls,** 40 ± 2.6 years old	2.1 ± 0.2 µg/g creatinine (2.5 ± 0.2 µg/l)	
Boffetta et al. 2001	6784♂, 265♀	**workers** (mercury mines and mills in Italy, Spain, Slovenia, Ukraine; not further specified) **control groups** (national reference mortality rates)	mercury mines < 1960: **1500 µg/l** > 1985: **100–300 µg/l** mercury mills < 1960: **300 and 500–600 µg/l, respectively** > 1980: **100–150 µg/l and 300 µg/l, respectively**	**mortality study** SMR (95 % CI) all cases 1.08 (1.04–1.12) hypertension 1.46 (1.08–1.93) renal diseases 1.55 (1.13–2.06) mine workers 1.71 (1.16–2.43) mill workers 1.39 (0.74–2.39) relative risk (RR) for renal diseases with increasing employment duration: RR (95 % CI) 1–9 years 1.0 10–19 years 3.3 (0.8–13.0) 20–29 years 4.7 (0.9–24.7) > 30 years 9.1 (1.6–52.6)

Abbreviations: AChE: acetyl cholinesterase; G6PD: glucose-6-phosphate dehydrogenase; GSH: glutathione; MCV: mean corpuscular volume; MCHC: mean corpuscular haemoglobin concentration; SCE: sister chromatid exchange; HPRT: hypoxanthine-guanine-phosphoribosyl transferase; RR: relative risk; SMR: standardized mortality ratio; SOD: superoxide dismutase