Hydrogen fluoride and inorganic fluorine compounds (fluorides) – Addendum for re-evaluation of the BAT value

Assessment Values in Biological Material – Translation of the German version from 2014

P. Lämmlein[1]

[1] Institute and Outpatient Clinic of Occupational, Social and Environmental Medicine, Friedrich-Alexander University (FAU) Erlangen-Nürnberg, Henkestraße 9–11, 91054 Erlangen, Germany

email: MAK Commission (arbeitsstoffkommission@dfg.de)

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BAT value (2013)	**4 mg fluoride/l urine** Sampling time: end of exposure or end of shift
MAK value (2005)	**hydrogen fluoride:** **1 ml/m³ ≙ 0.83 mg/m³** **fluorides:** **1 mg/m³ I (inhalable fraction)**
Absorption through the skin (2005)	hydrogen fluoride: – fluorides: H
Carcinogenicity	–

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Re-evaluation

The BAT values (biological tolerance values) of 7 mg fluoride/g creatinine [7664-39-3] at the end of exposure or end of shift and of 4 mg fluoride/g creatinine at the beginning of the next shift, established in 1983 (translated in Lewalter 1994) and re-evaluated in 2006 (translated in Schaller 2016), are defined as ceiling values and are re-evaluated following the introduction of the average value concept for BAT values (Drexler et al. 2008).

Since the last re-evaluation, no new studies on occupational exposures to fluoride have been published. An assessment of the clinical significance of the stages of skeletal fluorosis has been described by the Committee on Fluoride in Drinking Water (expert committee of the National Academy of Sciences) (NRC 2006):

Stage 0: Preclinical stage, increased bone density, fluoride content < 4 g/kg bone substance

Stage I: Sporadic pains, stiffness of the joints, mild osteosclerosis (for example pelvis and spinal column), increased bone density, fluoride content < 7 g/kg bone substance

Stage II: Chronic pains, arthritis, increased osteosclerosis with possible osteoporosis of the long tubular bones, characteristic: incipient or slight calcification of the ligaments, fluoride content < 9 g/kg bone substance

Stage III: Permanently restricted joint mobility, calcification of the ligaments, paralyzing deformities of the spinal column and joints ("crippling"), fluoride content > 8 g/kg bone substance

In the early stages (0 and I), the described clinical symptoms are non-specific. A clear diagnostic assignment is not possible until stage II, which is regarded by the Committee on Fluoride in Drinking Water as the initial health-damaging phase (NRC 2006).

Exposure and effects

Relationship between internal exposure and effects

The available publications on concentrations of fluoride in urine and symptoms of skeletal fluorosis are compiled in Table 1. In some of the studies (Derryberry et al. 1963; Dinman et al. 1976; Kaltreider et al. 1972), the internal fluoride exposure of the workers was determined over an extended period of time, for which reason they are the most suitable in assessing the long-term effects of fluoride. In the case of the studies by Chan-Yeung et al. (1983), Largent et al. (1951) and Zhiliang et al. (1987) on the other hand, the urine samples were collected only once. The collective in the study by Ando et al. (1998) were not occupationally exposed to fluoride but were exposed to fluorides in drinking water in the framework of an environmental medical study.

In a factory producing inorganic fluorides, workers, with an average internal exposure of 2.8 mg fluoride/l urine (range 0.96–5.28 mg/l urine; pooled urine), did not show signs of skeletal fluorosis. In workers exposed to a higher fluoride level (average value 12.4 mg/l urine, range 4.86–28.40 mg/l urine), a slight to marked increase in bone density and calcification of the ligaments was found (Largent et al. 1951).

Derryberry et al. (1963) investigated the effects of fluoride exposure on the health of workers at a factory producing phosphate fertilisers. After an average active working period of 14 years, indications of an increased occurrence of fluoride-induced osteosclerosis and in one case incipient calcification of the ligaments were found in workers exposed to fluorides with an average elimination of 5.18 mg fluoride/l urine (after the shift). In the workers exposed to fluorides in whom no indications of skeletal fluorosis were present, the average elimination was 4.53 mg fluoride/l urine. Non-exposed control persons were found to have average concentrations of 1.15 mg fluoride/l urine (Derryberry et al. 1963). From 1945 to 1950 and from 1960 to 1970, Kaltreider et al. (1972) carried out a study on the health and exposure to fluoride in workers at two aluminium smelters. In the first smelter, in 33% of the workers with an average elimination of 8.7–9.8 mg fluoride/l urine (after the shift) clear or advanced skeletal fluorosis was found which, according to the authors, had no adverse physiological effects (Kaltreider et al. 1972). Findings such as arthritis, increased osteosclerosis and calcification of the ligaments in some of the workers, however, correspond to phase II of skeletal fluorosis and are assessed by the Committee on Fluoride in Drinking Water as constituting adverse health effects (NRC 2006). In the second aluminium smelter, no signs of skeletal fluorosis were found at average concentrations of 1.4 mg fluoride/l urine (before the shift) and 3.0 mg fluoride/l urine (at the end of a working week) (Kaltreider et al. 1972).

In a follow-up examination of workers who had been employed at the same smelter for an average of 15 years, no skeletal changes were observed at a concentration of 2.78 mg fluoride/l in pre-shift urine and 7.71 mg fluoride/l in post-shift urine (Dinman et al. 1976).

Chan-Yeung et al. (1983) found no clear signs of skeletal fluorosis in workers at an aluminium smelter, who had been exposed to fluoride for longer than 10 years. In a number of highly exposed workers (2.0 mg/l pre-shift urine and 2.9 mg/l post-shift urine), radiographic examination revealed slightly increased bone density, calcification of the ligaments and periosteal changes. There was, however, poor agreement in the evaluation of the two radiologists who read the films. In the case of the workers with medium exposure (1.6 mg fluoride/l pre-shift urine and 1.4 mg fluoride/l post-shift urine), no changes were observed.

The study by Zhiliang et al. (1987) in 63 factories in the metallurgical industry showed an approximately 10-fold greater prevalence of increased bone density of workers with an average fluoride exposure of 0.3–7.5 mg/l in the pre-shift urine compared with control persons (0.25–1.8 mg/l urine). In the exposed persons, ossifications occurred twice more frequently, impaired joint mobility 3 to 4 times more frequently. Concentrations of up to 21 mg fluoride/l urine were found in the post-shift urine. Differential diagnosis between endemic and occupational skeletal fluorosis was, however, rendered more difficult by the fact that a considerable number of workers lived in areas with high fluoride content in their drinking water. The authors nevertheless describe a relationship between the occurrence of skeletal fluorosis and the duration of employment. This duration correlates with the severity of the symptoms. However, from the information given, it is not possible to reconstruct with accuracy as from what average elimination of fluoride indications of skeletal fluorosis were observed (Zhiliang et al. 1987).

In an environmental medical study, skeletal fluorosis was diagnosed in 42% of the investigated population with endemic fluoride exposure. The values, however, varied widely. On average, men had an exposure of 32.6 µM fluoride/mM creatinine (corresponding to about 6.6 mg/l urine), and women an exposure of 23.3 µM/mM creatinine (corresponding to about 4.7 mg/l urine) (Ando et al. 1998).

Tab. 1 Average fluoride concentrations in urine and symptoms of skeletal fluorosis. Exposure to fluorides in drinking water (Ando et al. 1998) and exposure at the workplace to hydrogen fluoride and fluorides

Field of industry/ collective	n[a)]	n_U[b)]	Average fluoride concentration in urine [mg/l]			n_SF[c)]	Symptoms of skeletal fluorosis	Phase SF[d)]	References
			Pre-shift	Post-shift	Other time				
Production of inorganic fluorides, factory A									Largent et al. 1951
a) fluoride-exposed workers (high exposure)	4	4			12.4[e)]	4	mild to markedly increased bone density in four workers, calcification of ligaments	≤ II	
b) fluoride-exposed workers (medium exposure)	6	6			2.8[e)]	3	normal bone density		
c) workers occasionally exposed to fluoride	5	5			1.8[e)]	3	normal bone density		
d) controls (office workers)	2	2			0.7[e)]	0			
Production of inorganic fluorides, factory B									
fluoride-exposed workers	6	6			6.5[e)]	6	markedly increased bone density in one worker with very high fluoride excretion	≤ II	

Tab. 1 *(continued)*

Field of industry/ collective	n[a)]	n_U[b)]	Average fluoride concentration in urine [mg/l]			n_SF[c)]	Symptoms of skeletal fluorosis	Phase SF[d)]	References
			Pre-shift	Post-shift	Other time				
Production of phosphate fertilisers									Derryberry et al. 1963
a) fluoride-exposed workers	74	74		4.7		74	hypertrophic arthritis in two workers, incipient calcification of the ligaments in one worker	≤ II	
with increased bone density	17	17		5.2		17		≤ II	
with normal bone density	57	57		4.5		57			
b) non-exposed controls	67	67		1.15		67	hypertrophic arthritis in one worker	≤ 0	
Aluminium smelter 1 (1945–1950)									Kaltreider et al. 1972
a) workers in the furnace/prebake potroom	107	107		8.7–9.8[f)]		79	increased bone density in 96% of the workers; clear or advanced skeletal fluorosis in 33% of the workers	≤ II	
b) non-exposed controls	108	108		0.7[f)]		0			
Aluminium smelter 2 (1960–1970)									
a) workers in the furnace/prebake potroom	284	281	1.4[g)]	3.0[h)]		231	–	–	
b) non-exposed controls	11	≤ 11	0.9	0.8		0			
Subsequent examination of the workers at aluminium smelter 2 investigated by Kaltreider et al. (1972)									Dinman et al. 1976
a) workers with high exposure		558[i)]	2.78			56[k)]	–	–	
		793[i)]		7.71					
b) all workers included		2336[i)]	2.24						
		3044[i)]		5.63					

Tab. 1 *(continued)*

Field of industry/ collective	n[a)]	n_U[b)]	Average fluoride concentration in urine [mg/l] Pre-shift	Post-shift	Other time	n_SF[c)]	Symptoms of skeletal fluorosis	Phase SF[d)]	References
Aluminium smelter									Chan-Yeung et al. 1983
a) workers with high exposure (oven area)	570	79–95	2.0	2.9	3.3[h)]	136	increased bone density ($n_A = 4/n_B = 3$), calcification of ligaments ($n_A = O/n_B = 4$) and periosteal changes ($n_A = 9/n_B = 0$)[l)]	≤ I	
b) workers with medium exposure (oven area)	332	5–15	1.6	1.4	1.7[h)]	41	–	–	
c) other exposures (e.g. maintenance)	284		1.5	1.8	1.9				
d) internal controls	880	25–30	1.1	1.2	1.1	33	periosteal changes ($n_A = 1/n_B = 0$)[l)]	≤ I	
Metallurgical industry (63 factories)									Zhiliang et al. 1987
a) fluoride-exposed workers	9624	9422	0.3–7.5	< 21		6224	increased bone density, osteosclerosis, impaired joint mobility, proliferation of trabeculae	≤ II	
b) controls	400	n. d.	0.3–1.8			845		≤ II[m)]	
Endemic areas for fluorides (China)									Ando et al. 1998
a) fluorosis area, China	2984 (♂)	53			6.6	5831	skeletal fluorosis in 42.10% of those investigated, severe osteosclerosis, increased bone density	≤ II	
	3516 (♀)	26			4.7				
b) control area, China	1027 (♂)	26			0.6			–	
	1055 (♀)	50			0.8				
c) control area, Japan	n. d.	36 (♂)			0.6			–	
		38 (♀)			1				

a) number of investigated persons
b) number of persons with at least one determination of fluoride in urine
c) number of persons with at least one examination for skeletal fluorosis
d) phase of skeletal fluorosis derived according to the criteria of the NRC (2006)
e) pooled urine (2–3 l)
f) workers came directly from work to the investigation; no data as to whether during or after the shift
g) after two free days
h) after five work days
i) determination of fluorides in urine over the period covering 1960–1974
k) comparison with previous findings by Kaltreider et al. (1972)
l) poor agreement in the findings by the two radiologists (radiologist A/radiologist B)
m) statistically significantly ($p < 0.01$) lower prevalence of individual phases of skeletal fluorosis compared with exposed persons
n. d. = no data

Re-evaluation of the BAT value

For evaluation of the BAT value, mainly the studies by Derryberry et al. (1963) and Kaltreider et al. (1972) are used. These studies are best suited for assessment of the long-term effects of fluorides, as the internal exposure of the workers to fluorides was determined over an extended period of time. According to the results of the study by Derryberry et al. (1963) an average excretion of 4 mg fluoride/l post-shift urine can be tolerated for long periods without expecting fluorine-induced skeletal changes to occur. The results of the studies by Ando et al. (1998), Chan-Yeung et al. (1983), Kaltreider et al. (1972) and Largent et al. (1951) confirm this estimate. Only in the study by Dinman et al. (1976), no skeletal fluorosis was observed at a concentration of 7.7 mg fluoride/l post-shift urine.

Therefore, according to the average value concept (Drexler et al. 2008),

a BAT value of 4 mg fluoride/l urine

is established.

Sampling should be carried out at the end of exposure or the end of the shift.

The value given is not related to creatinine, as the results are given in mg/l urine in the original studies on which the derivation of this BAT value is based.

The BAT value of "4 mg fluoride/g creatinine at the beginning of next shift" is withdrawn.

Interpretation

The BAT value relates to normally concentrated urine, in which the creatinine concentration should be in the range of 0.3–3 g/l. In addition to this, the Commission considers it useful, for further improving the validity of the analyses, to select a narrower target range of 0.5–2.5 g/l for urine samples. As a rule, where urine samples are outside the above limits, a repetition of the measurements in normally hydrated test persons is recommended (Bader et al. 2016).

The creatinine level should be monitored especially at hot workplaces.

Notes

Competing interests

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

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