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GMS PUBLISSO ZB MED-Publikationsportal Lebenswissenschaften

Hydrogen fluoride and inorganic fluorine compounds (fluorides) – Addendum: Evaluation of a pregnancy risk group for the BAT value

Assessment Values in Biological Material – Translation of the German version from 2023

Keywords

hydrogen fluoride and inorganic fluorine compounds (fluorides); biological tolerance value; BAT value; developmental toxicity; prenatal toxicity

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Citation Note:
Michaelsen S, Schriever-Schwemmer G, Drexler H, Hartwig A, MAK Commission. Hydrogen fluoride and inorganic fluorine compounds (fluorides) – Addendum: Evaluation of a pregnancy risk group for the BAT value. Assessment Values in Biological Material – Translation of the German version from 2023. MAK Collect Occup Health Saf. 2023 Mar;8(1):Doc022. https://doi.org/10.34865/bb766439e8_1ad

Manuscript completed:
01 Feb 2022

Publication date:
30 Mar 2023

Abstract

In 2005, the German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area re-evaluated the maximum workplace concentration (MAK value) of hydrogen fluoride [7664-39-3] and fluorides [16984-48-8]. If the MAK values of 1 ml hydrogen fluoride/m^3 (0.83 mg/m^3) or 1 mg fluoride/m^3, respectively, are not exceeded, prenatal toxic effects are not to be expected. Therefore, hydrogen fluoride and fluorides were classified in Pregnancy Risk Group C. In 2013, the biological tolerance value (BAT value) for hydrogen fluoride and inorganic fluorine compounds (fluorides) of 4 mg fluoride/l urine was established which protects against the long-term effects of fluoride such as skeletal fluorosis. The BAT value was not derived in correlation to the MAK value. For this reason, it is to be evaluated whether no prenatal toxic effects are to be expected when the BAT value is adhered to. By extrapolating the NOAEL (no observed adverse effect level) for developmental toxicity in rodent studies to fluoride concentrations in urine it could be concluded that Pregnancy Risk Group C is also valid for the BAT value.

BAT value (2013)	**4 mg fluoride/l urine** Sampling time: end of exposure or end of shift
Prenatal toxicity (2022)	Pregnancy Risk Group C
MAK value (2005)	**Hydrogen fluoride:** **1 ml/m³ ≙ 0.83 mg/m³** **Fluorides:** **1 mg/m³ I (inhalable fraction) as fluoride**
Absorption through the skin	Hydrogen fluoride: – Fluorides (2005): H

In 2005, maximum workplace concentrations (MAK values) of 1 mg/m³ I (inhalable fraction) for fluorides and 1 ml/m³ (≙ 0.83 mg/m³) for hydrogen fluoride were derived. Since, based on the available data for exposures at the level of these MAK values, prenatal toxic effects are not to be expected, if the MAK values are not exceeded, hydrogen fluoride and fluorides were classified in Pregnancy Risk Group C (Hartwig 2014 b, 2015). In 2013, a biological tolerance value (BAT value) of 4 mg fluoride/l urine for hydrogen fluoride and inorganic fluorine compounds (fluorides) was established, which protects against the long-term effects of fluoride such as skeletal fluorosis (Lämmlein 2021). The BAT value was not derived in correlation to the MAK value. For this reason, it is to be evaluated whether no prenatal toxic effects are to be expected when the BAT value is adhered to and whether Pregnancy Risk Group C is also valid for the BAT value.

Prenatal toxicity

The available literature on the prenatal toxic effects has been re-evaluated. Reliable human studies are not available.

Developmental toxicity

From a prenatal developmental toxicity study in Sprague Dawley rats with drinking water administration of sodium fluoride from gestation days 6 to 15, a NOAEL for developmental toxicity of 13.2 mg fluoride/kg body weight and day, the highest dose tested, can be derived. At this dose level, drinking water intake was reduced in the dams due to poor palatability (Hartwig 2014 a, 2015; Heindel et al. 1996).

In another prenatal developmental toxicity study in CD-CRL:CD-BR, VAF+ rats, the two high sodium fluoride concentrations of 175 and 250 mg/l drinking water (11.1 and 11.3 mg fluoride/kg body weight and day) led to decreased drinking water intake. At the highest dose tested, concomitant maternal toxicity (decreased food intake and decreased body weight gains) resulted in a small but statistically significant increase in the incidence of foetuses with skeletal variations (0.4 affected foetuses per litter compared with 0.1 in the control). The percentage of affected litters was increased (21.6% compared with 8.8% in the control) but not at a statistically significant level (Collins et al. 1995; Hartwig 2014 b, 2015). The NOAEL for developmental and maternal toxicity is thus 11.1 mg fluoride/kg body weight and day (Hartwig 2015).

A NOAEL for developmental toxicity of 175 mg/l (equivalent to 9.7 mg fluoride/kg body weight and day) was derived from a one-generation study in CD-CRL:CD-BR rats with drinking water administration of sodium fluoride. This NOAEL was based on an increased incidence of F2 foetuses with delayed ossification of the hyoid bone at 250 mg sodium fluoride/l (12.5 mg fluoride/kg body weight and day). There was a concomitant statistically significant decrease in the body weights and in food and water consumption in the dams. The F1 foetuses did not exhibit ossification delays of that kind (Collins et al. 2001; Hartwig 2015).

A prenatal developmental toxicity study in New Zealand rabbits with drinking water administration of sodium fluoride from gestation days 6 to 19 yielded a NOAEL for developmental toxicity of 13.8 mg fluoride/kg body weight and day, which corresponded to the highest dose tested. At this dose, in the dams, reduced water intake and temporarily reduced

food intake and decreased body weights (6th to 8th day of gestation) were observed (Hartwig 2014 b, 2015; Heindel et al. 1996).

Teratogenic effects were not seen in any of these studies.

Evaluation of a pregnancy risk group for the BAT value

In summary, in the studies on prenatal developmental toxicity, no developmental toxic effects were observed despite maternal toxicity up to dose levels of 11.1 and 13.2 mg fluoride/kg body weight and day (175 and 300 mg sodium fluoride/l drinking water) in rats and up to 13.8 mg fluoride/kg body weight and day (400 mg sodium fluoride/l drinking water) in rabbits (Collins et al. 2001; Hartwig 2015; Heindel et al. 1996). The magnitude of the ingested doses was limited due to poor palatability of sodium fluoride in drinking water. In a one-generation study in CD-CRL:CD-BR rats with drinking water administration of sodium fluoride, there was an increased incidence of F2 foetuses with delayed ossification of the hyoid bone at 250 mg sodium fluoride/l (12.5 mg fluoride/kg body weight and day) with concomitant maternal toxicity. The NOAEL for developmental toxicity was 175 mg/l (corresponding to 9.7 mg fluoride/kg body weight and day) (Collins et al. 2001; Hartwig 2015). This NOAEL is to be regarded as conservative due to the absence of such an effect in the F1 generation.

With MAK values of 1 mg fluoride/m^3 I for fluorides and 1 ml/m^3 (0.83 mg/m^3) for hydrogen fluoride, these substances were assigned to Pregnancy Risk Group C. Since the BAT value was not derived in correlation to the MAK value, it is to be evaluated whether also no prenatal toxic effects are to be expected when the BAT value for hydrogen fluoride and inorganic fluorine compounds (fluorides) is adhered to.

Determinations of the fluoride concentration in the urine of pregnant rats or rabbits are not available.

In a carcinogenicity study by the NTP with administration of 175 mg sodium fluoride/l (4.5 mg fluoride/kg body weight and day in the drinking water; Bucher et al. 1991), the fluoride concentrations in the urine of female rats at the interim examinations after 27 and 66 weeks were 33.0 and 26.8 mg fluoride/l, respectively. The corresponding control values at these time points were 1.1 and 0.9 mg fluoride/l, respectively (NTP 1990). There was thus an increase in the fluoride concentrations in the urine of up to about 30-fold. For the most conservative NOAEL of 9.7 mg fluoride/kg body weight and day from the one-generation study (Collins et al. 2001; Hartwig 2015), a fluoride concentration in urine of about 71 mg fluoride/l can be calculated using the data from the NTP study (9.7 mg/kg body weight/4.5 mg/kg body weight × 33 mg/l urine). The margin to the BAT value of 4 mg fluoride/l urine is thus almost 18-fold.

Therefore, if the BAT value of 4 mg fluoride/l urine is adhered to no prenatal toxic effects are to be expected.

The assignment of hydrogen fluoride and inorganic fluorine compounds (fluorides) to Pregnancy Risk Group C is therefore also valid for the BAT value.

Notes

Competing interests

The established rules and measures of the commission to avoid conflicts of interest (www.dfg.de/mak/conflicts_interest) ensure that the content and conclusions of the publication are strictly science-based.

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