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Isoflurane – Evaluation of a BAT value

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

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Abstract

The German Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area re-evaluated isoflurane [26675-46-7] and a maximum concentration at the workplace (MAK value) of 2 ml/m^3 has been set for isoflurane. The substance is used as a volatile anaesthetic, and absorption of isoflurane at the workplace is by inhalation. Human studies are not available to derive a quantitative relationship between the internal dose and the critical toxic effects of isoflurane (neurotoxicity and liver toxicity, effects on reproductive organs). Three studies on surgical employees show a linear correlation between the concentration of isoflurane in the air and urine concentration. In correlation to the MAK value of 2 ml/m^3, a biological tolerance value (BAT value) of 4 µg isoflurane/l urine was established. Sampling time is at the end of exposure or end of shift. There are no studies in neonatal or juvenile animals at non-anaesthetic concentrations to derive a no observed adverse effect concentration (NOAEC) for developmental neurotoxic effects of isoflurane. Therefore, isoflurane was assigned to Pregnancy Risk Group D. Since the BAT value was derived in correlation to the MAK value, Pregnancy Risk Group D also applies to the BAT value.

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BAT value (2022)	**4 µg/l urine** Sampling time: end of exposure or end of shift
MAK value (2021)	**2 ml/m³ (ppm) ≙ 15 mg/m³**
Peak limitation (2021)	Category II, excursion factor 8
Absorption through the skin	–
Sensitization	–
Carcinogenicity	–
Prenatal toxicity (2021)	Group D
Germ cell mutagenicity	–

For isoflurane, documentation from 1993 (translated in Greim 1996) and an addendum from 2007 (translated in Hartwig and MAK Commission 2016) are available. In 2021, a MAK value of 2 ml/m³ was derived (Hartwig and MAK Commission 2022).

1 Metabolism and toxicokinetics

The data on kinetics are described in detail in the 1993 documentation (Greim 1996) and in the 2007 addendum (Hartwig and MAK Commission 2016).

1.1 Absorption and distribution

Absorption of isoflurane at the workplace is by inhalation. In 10 healthy pregnant women, isoflurane concentrations of 24 mg/l blood and 70 mg/l cord blood were determined after isoflurane anaesthesia with 6000 ml/m³ (NEG 2009).

Due to the high vapour pressure, exposure to liquid isoflurane is very unlikely. The proportion of isoflurane absorbed through the skin by rats at an external concentration of 50 000 ml/m³ is 0.1% of the amount absorbed by inhalation (McDougal et al. 1990).

The half-life of isoflurane in the well perfused organs such as brain, liver, heart and kidneys is given as approx. 20 minutes, so that after approx. 100 minutes (5 half-lives) the steady state should be reached (Greim 1996; Hartwig and MAK Commission 2016).

The partition coefficients of isoflurane in humans are given in Table 1.

Tab. 1 Partition coefficients of isoflurane in humans

Blood:Air Pc	Urine:Air Pc	Fat:Air Pc	Tissue:Air Pc				
			Brain	Liver	Kidney	Muscle	Heart
1.42[a)]	0.72[b)]	69.68[a)]	2.23[a)]	3.12[a)]	1.75[a)]	3.01[a)]	2.2[c)]

Pc: Partition coefficient
[a)] Meulenberg and Vijverberg 2000
[b)] Accorsi et al. 2001
[c)] NEG 2009

1.2 Metabolism

After surgical interventions with isoflurane as an anaesthetic, less than 0.2% of the fluorine taken in as isoflurane is found in the form of fluoride in the urine (Holaday et al. 1975). Trifluoroacetic acid and fluoride have been identified as end products of metabolism, with trifluoroacetic acid being the main metabolite (approx. 137 mg/day after exposure to 9000 ml/m^3 for 2.8 hours; determined in the 24-hour urine of the day of exposure) in humans (Hitt et al. 1974).

2 Critical toxicity

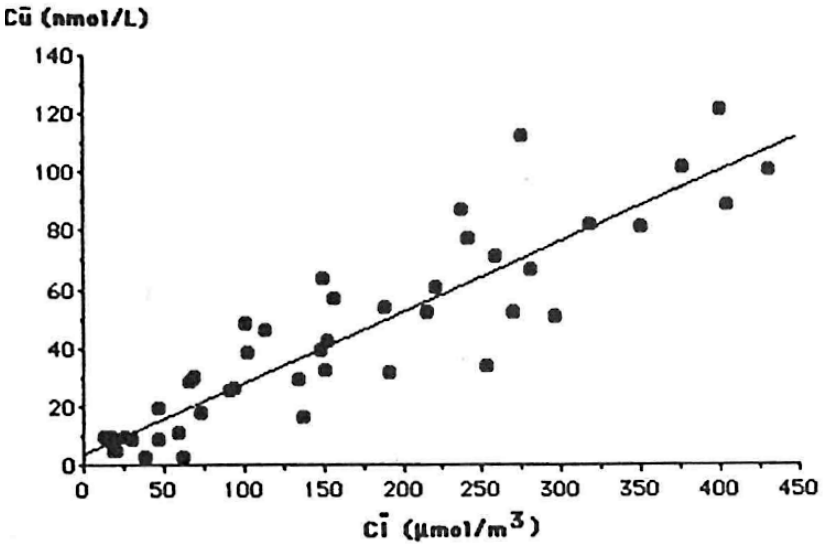
The most sensitive end points are neurotoxicity in humans and liver toxicity and effects on the reproductive organs in animals. Neurotoxicity studies in surgical workers exposed to isoflurane and nitrous oxide (N_2O) provided no evidence of a neurotoxic effect of isoflurane at a median isoflurane concentration of 0.5 ml/m^3 and a maximum of 24.1 ml/m^3. At best, an indication of a genotoxic potential of isoflurane is given by the cross-sectional studies on DNA damage in surgical personnel. However, since there was a mixed exposure to different inhalation anaesthetics in the operating rooms, the previous exposure to other inhalation anaesthetics was not reported and the biostatistics are in some cases unclear, a specific genotoxic effect of isoflurane cannot be deduced from the available studies. The results of studies on DNA damage performed during or after anaesthesia with isoflurane during minimally invasive surgery in patients without pre-existing conditions were negative (see also Hartwig and MAK Commission 2022).

3 Exposure and Effects

3.1 Relationship between external and internal exposure

There are several studies on the correlation between the concentration of isoflurane in air and urine, which are described below (see also Table 2).

The air concentrations of nitrous oxide, enflurane and isoflurane were determined for four hours from a total of 45 employees in the operating theatre area (28 men and 17 women from anaesthesia, surgery and nursing). The measurements were taken in 11 operating theatres of 5 hospitals in Italy. The age of the workers was given as 43 ± 12 years. The geometric mean isoflurane concentration in air was 112.8 µmol/m^3 (2.7 ml/m^3; geometric standard deviation (GSD): 2.609; range: 14.6–441 µmol/m^3 (0.4–10.9 ml/m^3); limit of detection (LOD): 1 µmol/m^3). The geometric mean isoflurane concentration in urine determined at the end of the exposure period was 28.8 nmol/l (GSD: 2.877; 5.3 µg/l). In a control group of 10 unexposed workers at a university hospital, no isoflurane was detected in the urine. The concentrations of isoflurane in air correlated with statistical significance with the concentrations in urine. Since the intercept of the regression line with the y-axis was greater than zero at 3.7 nmol/l (0.7 µg/l), the authors suspected that workers did not metabolize all isoflurane overnight and considered this value as a pre-shift value. A correlation results from the data of the study. Using the corresponding regression equation C_u [nmol/l] = 0.24 × C_i [µmol/m^3] + 3.71, exposure at the MAK value of 2 ml isoflurane/m^3 (83 µmol/m^3) results in a concentration of 23.63 nmol isoflurane/l urine (4.36 µg/l) for a 4-hour exposure. Using the lower 95% confidence limit of the regression line via the equation C_u = 0.216 × C_i + 0.90, the concentration in urine is 3.47 µg isoflurane/l (Figure 1, Imbriani et al. 1988).



C_u [nmol/l] = 0.24 × C_I [µmol/m³] + 3.71 (r = 0.904; n = 45; p < 0.0001)

Fig. 1 Correlation between isoflurane concentration in air (c_i) and in urine (c_u) (from Imbriani et al. 1988; reproduced by permission of Taylor & Francis Ltd, http://www.tandfonline.com)

In another study by the same working group, personal air concentrations of nitrous oxide, halothane, enflurane and isoflurane and the corresponding urine concentrations were determined over four hours in 1521 workers (1138 men, 383 women) in the operating theatre area (anaesthesia, surgery, nursing). The determinations were made in 190 operating theatres of 41 hospitals in Italy. The age of the workers was given as 42.6 ± 9.3 years. The concentrations of isoflurane were 1.01 ml/m³ (GSD: 3.69; range: 0.1–9.6 ml/m³) in air and in urine 3.483 µg/l (GSD: 3.58; range: 0.1–38.7) in a total of 362 determinations (Imbriani et al. 1995). At the beginning of the shift, no isoflurane was detected in the urine of the exposed persons (LOD: 0.1 µg/l urine), nor in a control group of 20 non-exposed employees of a university hospital. From the correlation between the isoflurane concentrations in the air at the workplace and in the urine, a urine concentration of 6.9 µg isoflurane/l is calculated via the regression equation C_u [µg/l] = 2.987 × C_i [ml/m³] + 0.94 (p < 0.0001) at the MAK value of 2 ml/m³. Using the lower 95% confidence limit, a concentration of 5.3 µg isoflurane/l urine is calculated.

Urinary and airborne isoflurane concentrations were determined in 45 workers (5 anaesthetists, 5 surgical nurses, 15 anaesthesia technicians, 20 operating theatre technicians) in 9 operating theatres. The study was divided into two parts: in the first part, personal and stationary measurements of air concentrations (for 2 to 6 hours, depending on the duration of the surgery) were performed and 45 urine samples were taken at the end of the shift. In the second part of the study, the isoflurane concentration in ambient air was measured every 30 minutes for 6 hours to determine if there was an increase in concentration over the shift. These measurements were taken in three different weeks with different workloads. A mixture of oxygen, nitrous oxide, isoflurane and sevoflurane was used as anaesthetic. Geometric means of personal concentrations of 1.41 ml isoflurane/m³ (GSD: 2.27; median: 1.33; range: 0.27–8.21) and of stationary concentrations of 2.3 ml isoflurane/m³ (GSD: 2.43; median: 2.76; range: 0.38–10.41) were determined in the air. The stationary concentrations tended to be higher than the person-related. Air concentrations increased to 10 ml/m³ in the last two hours of exposure and reached peak concentrations of more than 20 ml/m³ in the last half hour. No statistically significant differences in urine and air concentrations were observed in relation to the activity performed. The geometric mean concentration in urine was 2.42 µg/l (GSD: 2.86; median: 2.33; range 0.31–13.38 µg/l). A statistically significant correlation with a coefficient of determination r^2 of 0.724 (p < 0.0001) was found for the concentrations in air and urine (Jafari et al. 2018). To convert the concentrations from a 2- to 6-hour shift to an 8-hour time-weighted mean they were multiplied by the corresponding shift duration and divided by 480 minutes. These calculated concentrations

were used to create the regression line (Jafari 2022). From the given correlation equation logy [µg/l] = 1.138 logx + 0.215, a concentration of 3.61 µg/l urine is calculated for the MAK value of 2 ml/m³.

In the publications by Accorsi et al. (2001) and Scapellato et al. (2008), only data on isoflurane concentrations in urine are given, but not on concentrations in ambient air (see Table 2).

Tab. 2 Determination of isoflurane in urine

Number exposed Sample number	Exposure duration air concentration [ml/m³]	Isoflurane in urine [µg/l]			References
		Mean value (SD)	Median	Range	
11 operating theatres, 5 hospitals, 45 employees (28 ♂, 17 ♀), age 43 ± 12 years, Exposure measurements in 7 clinics	4 h, person-related: 112.8 µmol/m³ (2.609)[b] (≙ 2.8 ml/m³), range: 14.6–441 µmol/m³ (≙ 0.4–10.9 ml/m³) LOD: 1 µmol/m³	28.8 nmol/l (2.877)[b] (≙ 5.3 µg/l)	no data	2.02–121 nmol/l (0.4–22.3 µg/l)	Imbriani et al. 1988
190 operating theatres, 41 hospitals, 1521 employees (1138 ♂, 383 ♀), age 42.6 ± 9.3 years, Exhaust air in 23 operating theatres, 362 samples	4 h, person-related: 1.01 (3.69)[b], range: 0.1–9.6	3.48 (3.58)[b]	no data	0.1–38.7	Imbriani et al. 1995, 1998
45 persons (5 anaesthetists, 15 anaesthesia technicians, 20 operating theatre technicians, 5 nurses)	2–6 h, person-related: 1.84 (1.92)[a]; 1.41 (2.27)[b] (median 1.33; range: 0.27–8.21) stationary: 3.18 (1.92)[a] ; 2.3 (2.43)[b] (median: 2.76; range: 0.38–10.41)	3.58 (2.71)[a] 2.42 (2.86)[b]	2.33	0.31–13.38	Jafari et al. 2018
701 samples	3 h, early shift, no data	0.6 (0.2)	0.1	0.0–36.0	Accorsi et al. 2001
38 exposed, 23 control persons	7 h, 12 min, no data	Monday: 1.1 (2); Friday: 1.34 (1.89)	no data no data	0.3–4.7 0.1–4.7	Scapellato et al. 2008

LOD: limit of detection
[a] arithmetic mean (SD)
[b] geometric mean (GSD)

3.2 Relationship between internal exposure and effects

In a cohort study of 52 persons (anaesthesia, surgery, nursing) in a clinic in Iran, the liver and nephrotoxicity of anaesthetic gases was investigated. The control group consisted of 52 unexposed employees from the hospital administration whose age, weight, height, body mass index (BMI) and duration of employment matched those of the exposed. The mean duration of employment was reported as 10.79 ± 5.63 years (exposed) and as 8.69 ± 6.57 years (control persons). The following were determined in the serum: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), γ-glutamyl transferase (γ-GT), albumin, total protein, bilirubin, urea, creatinine, calcium, phosphorus, potassium, α-glutathione S-transferase (α-GST) and KIM-1 (type 1 transmembrane glycoprotein: biomarker for nephrotoxicity). Urine samples were analysed after the three-hour morning shift in the operating theatre. In urine, the concentration of isoflurane was 4.95 ± 3.43 µg/l (the unit ppm (mg/l) given in the publication was corrected to µg/l by the authors (Neghab et al. 2021)) (range: 0.78–14.9), of nitrous oxide 175.8 ± 77.52 µg/l (range: 7.98–319.91) and of sevoflurane 15.03 ± 16.06 µg/l (range: 0.76–46.40). After adjusting for age, sex and BMI, serum AST, ALT, γ-GT, α-GST, creatinine, KIM-1 and calcium were elevated with statistical significance in exposed subjects compared with the values in the controls (Neghab et al. 2020). The study cannot be used to evaluate liver and kidney parameters altered

by isoflurane exposure, as the operating theatre personnel were exposed to other inhalation anaesthetics and the reliability of the adjustment for alcohol consumption is doubtful.

The following studies on the relationship between altered liver enzymes in the blood and exposure to inhalation anaesthetics are not considered in the evaluation due to lack of exposure assessment: Caciari et al. (2013), Franco et al. (1993), Saurel-Cubizolles et al. (1992).

4 Selection of indicators and research methods

Based on several studies with statistically significant correlations between external exposure to isoflurane in the air and the concentration of isoflurane in urine, isoflurane in urine is used as parameter. For the determination of the isoflurane concentration in urine, a headspace GC-MS method is currently being developed by the Commission's Working Group "Analyses in Biological Material". Fluoride determination to quantify isoflurane exposure is less suitable because of possible interfering influences.

5 Background exposure

There is no background exposure to isoflurane.

6 Evaluation of a BAT value

There are no studies available from which a correlation between internal exposure and effects can be deduced.

Based on the linear correlation between the concentration of isoflurane in air and isoflurane in urine described in Section 3.1 in three studies, a BAT value is derived in correlation to the MAK value. From the 95% lower confidence limits of 3.47 µg/l and 5.3 µg/l (Imbriani et al. 1988, 1995) after 4 hours of exposure and the concentration of 3.61 µg/l (Jafari et al. 2018) after 8 hours of TWA exposure at the level of the MAK value of 2 ml/m³ (Table 3) results a mean value of 4 µg isoflurane/l urine.

Tab. 3 Isoflurane concentrations in urine at the end of the shift at the MAK value of 2 ml/m³

Exposure duration	Isoflurane in urine at 2 ml/m³	References
4 h	4.36 µg/l (total) 3.47 µg/l (lower 95% confidence limit)	Imbriani et al. 1988
4 h	6.91 µg/l (total) 5.30 µg/l (lower 95% confidence limit)	Imbriani et al. 1995
8 h TWA (exposure 2–6 h)	3.61 µg/l (total)	Jafari et al. 2018

Therefore, in correlation to the MAK value of 2 ml isoflurane/m³, a

BAT value of 4 µg isoflurane/l urine

is derived. The sampling time is at the end of exposure or end of shift.

6.1 BAT value and pregnancy

There are no studies in neonatal or juvenile animals with non-anaesthetic concentrations from which a NOAEC (no observed adverse effect concentration) for developmental neurotoxic effects of isoflurane could be derived. Therefore, isoflurane has been assigned to Pregnancy Risk Group D. Since the BAT value was derived in correlation to the MAK value, Pregnancy Risk Group D also applies to the BAT value.

7 Interpretation

The BAT value refers to normally concentrated urine, in which the creatinine content should be in the range of 0.3 to 3 g/l. As a rule, for urine samples outside the above limits, it is recommended to repeat the measurement in the normally hydrated test person (translated in Bader et al. 2016).

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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