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Indium and its inorganic compounds – Evaluation of assessment values in biological material

Assessment Values in Biological Material – Translation of the German version from 2024

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Abstract

The German Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission) summarized and evaluated the data for indium [7440-74-6] and its inorganic compounds to derive a biological guidance value (BLW) or a biological reference value (BAR) considering all toxicological end points. Relevant studies were identified from a literature search. Herein, background concentrations in serum of control sample donors were compared with those of exposed workers. Only one publication reported values in urine aside from serum values, both showing no correlation to indium concentrations in air. None of the studies detected any relationship between external and internal exposure. It was also not possible to derive a concentration at which toxicity occurs. Background concentrations reported in several studies overlapped with the serum indium concentrations from other studies of exposed subjects having already significant adverse effects. An explanation cannot be deduced from the available data. The relevant concentrations furthermore are very low, meaning that laboratories have to work close to their limits of quantitation, which consequently leads to a high error scattering. Accordingly, no BLW and no BAR could be derived.

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BAR (2022)	**not established**
BLW (2022)	**not established**
Formula	In
Molar mass	114.818 g/mol
Melting point	157 °C (ECHA 2021)
Boiling point	2080 °C (ECHA 2021)
Density at 20°C	7.29 g/cm^3 (ECHA 2021)
MAK value	–
Absorption through the skin (2023)	H
Carcinogenicity (2023)	Category 2
Germ cell mutagenicity (2023)	Category 3B

General properties

Occurrence and extraction

Indium is a rare element, its share in the continental earth's crust is only 0.05 mg/kg. The theoretical reserves are estimated at 16,000 tonnes, of which about 11,000 tonnes are economically exploitable. In 1982, only about 50 tonnes of indium were produced worldwide, but production has increased dramatically since the dissemination of LCD screens (televisions, monitors, mobile phones). The largest deposits of indium are in zinc ores, especially sphalerite. It is extracted from residues from cadmium, lead and zinc smelting among others. Secondary production, i. e. recycling, now exceeds primary production and amounted to 800 tonnes in 2008 (ISE 2022).

Physical properties

The following compounds of trivalent indium are of interest: $InCl_3$, $In_2(SO_4)_3$, In_2O_3, $In(OH)_3$, and the intermetallic compounds InAs, InSb, InSe and InP. Only the chloride and the sulphate are readily soluble in water. Organoindium compounds are also described in the literature, e. g. trimethyl indium (see also Hartwig and MAK Commission 2024).

From 1987 onwards, two new indium compounds were developed, the semiconductor indium phosphide (InP) and the electrically conductive indium tin oxide (ITO), which is transparent in thin layers. ITO in particular became technically interesting with the development of liquid crystal displays and touch screens. Due to the high demand, most of the indium has been processed into ITO since 1992 (ISE 2022).

Metabolism and toxicokinetics

For detailed information on the metabolism and toxicokinetics of indium, see Hartwig and MAK Commission (2024).

Absorption

Absorption by inhalation of production dusts is considered the main uptake pathway.

Indium is absorbed from the gastrointestinal tract in humans only in less than 2% or in rats in less than 0.1% to approx. 0.5% of the applied $^{114}InCl_3$ dose (Bertram et al. 1991).

In the study by Brock et al. (2014), it was shown in female BALB/c-mice that unsintered ITO can penetrate both intact and damaged skin.

Distribution

After intravenous injection of indium in mice in the form of soluble In^{3+} compounds, the highest levels were found in the kidneys, whereas colloidal indium accumulated in the liver and spleen (Castronovo and Wagner 1971). In a 14-week inhalation study with indium phosphide in male rats, the indium concentration in the testes – unlike in the blood – also increased after the end of exposure, indicating a redistribution (NTP 2001). After 26 weeks of inhalation exposure to 0.1 mg ITO/m^3, indium was detected in extrapulmonary tissues such as spleen, kidneys, liver, bone marrow, pancreas, testes, ovaries and blood in male and female rats (Nagano et al. 2011).

Elimination

Ionic indium is largely eliminated via the kidneys, colloidal indium oxide via the intestines.

In workers exposed to indium oxide and ITO in an indium-producing factory, a half-life for indium in serum of 8.09 years was determined (Amata et al. 2015). The median half-life in the group with the highest serum level (> 10.0 µg/l) was 8.95 years (7.49–12.21), which was longer than in the groups with lower indium serum levels (5.80 and 6.63 years, respectively).

Toxicity

Whereas no toxic effects are known from native indium metal, indium ions showed mainly lung-damaging effects in animal experiments. Indium nanoparticles also caused lung-damaging effects, especially after partial solubilisation and conversion into In^{3+}-ions. Insoluble indium compounds are much less toxic after oral administration. Further information can be found in Hartwig and MAK Commission (2024).

Animal experiments

Lung-damaging effects including lung carcinogenicity have been clearly demonstrated in animal experiments after exposure of rats and mice to indium phosphide and ITO (Greim 2004). After intratracheal application of indium arsenide, inflammation and specific lesions appeared in the lungs of hamsters, which were apparently precancerous lesions with keratinisation to squamous cell cysts (Yamazaki et al. 2000).

Toxic effects in humans

Exposure at the workplace

Tanaka et al. (2010) reported cases of lung diseases, mainly interstitial pneumonias, caused by inhaled ITO or other indium compounds (see Table 1). In 2003, the first interstitial pneumonia caused by occupational exposure to ITO was reported in Japan. The patient died of bilateral pneumothorax in 2001. Histopathological examination of the lung

revealed that numerous fine particles had been deposited throughout the lung. The serum indium level was 290 µg/l (Homma et al. 2003). After the first case report, a second case of lung disease associated with inhaled ITO was reported in 2005. This worker developed pulmonary fibrosis and emphysema after 4 years of occupational exposure to ITO. The serum indium level was 51 µg/l. After leaving the workplace with possible ITO exposure and moving to another area, he showed no further progression of the lung disease (Homma et al. 2005).

Chonan et al. (2007) reported interstitial lung disease in 108 indium-processing workers exposed to tin oxide, indium oxide and ITO. Twenty-three workers showed interstitial lung changes and 40 workers displayed elevated serum levels (> 500 U/ml) of the marker "Krebs von den Lungen-6" (KL-6). The serum indium level correlated positively with the KL-6 level and with the degree of lung changes in the high-resolution computed tomography (HRCT). KL-6 is a mucin-like, high molecular weight glycoprotein expressed on the surface membrane of alveolar epithelial cells and bronchiolar epithelial cells, which is determined in the diagnosis of interstitial lung diseases.

Amata et al. (2015) conducted a follow-up study of the Chonan et al. (2007) collective. Eighty-four workers with high indium exposure were observed in this longitudinal study for 9 years from 2002 to 2010. Due to improved working conditions, serum indium concentrations, KL-6 levels and Surfactant protein-D (SP-D) concentrations decreased. The biological half-life of indium in serum was estimated to be 8.09 years. Longer half-lives were found at higher exposures. The total group had indium levels in serum between 0.2 and 126.7 µg/l. Airborne concentrations were also reported, decreasing from 0.1–1 mg/m^3 (2001) to 1–10 µg/m^3 (2010 and 2011). The HRCT showed partial regression of interstitial lesions, while emphysematous lesions progressively increased in workers with high serum indium concentrations ≥ 22.5 µg/l. The FEV1/FVC ratio (forced expiratory volume in one second/forced vital capacity = relative one-second capacity, proportion of the total maximum exhaled air, that can be exhaled in one second) decreased over the years, with a higher average yearly decline among workers with high serum indium levels.

In a cross-sectional study, Hamaguchi et al. (2008) examined 93 exposed persons from ITO production and 93 non-exposed persons. In the exposed workers, the parameters of pulmonary toxicity were statistically significantly elevated compared with those in the control subjects (KL-6: 495.4 vs. 240.1 U/ml; SP-D: 85.2 vs. 51.7 ng/ml; SP-A: 39.6 vs. 33.8 ng/ml). Surfactant protein-A (SP-A) and SP-D are considered sensitive markers for interstitial lung disease. The geometric mean concentrations of indium in serum were 8.25 µg Indium/l in the exposed and 0.25 µg Indium/l in the unexposed. Air concentrations of indium compounds were not reported. There were no differences between exposed and non-exposed workers as regards spirometry, subjective symptoms and the prevalence of interstitial or emphysematous changes on the lung HRCT.

Nogami et al. (2008) examined 40 indium-exposed workers and observed no interstitial changes in the lungs, but emphysematous changes in four individuals and lung cancer in one worker. Nine exposed workers had KL-6 levels > 500 U/ml. The exposed individuals with serum indium levels > 3 µg/l were exposed for a statistically significantly longer period (50.0 ± 16.8 months) and had statistically significantly higher KL-6 levels (588.3 ± 187.9 U/ml) than the workers with serum indium levels < 3 µg/l (exposure: 29.3 ± 28.1 months, KL-6: 261.0 ± 149.9 U/ml). A positive correlation (r = 0.73) was observed between serum indium levels and KL-6 levels.

In the study by Liu et al. (2012), 170 employees exposed to indium from two ITO manufacturing plants in Taiwan and 132 persons from the administration were examined. Average indium levels of 1.26 ± 3.09 µg/l were determined in the serum of the indium-exposed workers and 0.72 ± 2.4 µg/l in the serum of the administrative workers. Forty-nine of the examined exposed persons had serum indium levels of more than 3 µg/l. Significant positive correlations were observed between indium in serum and the levels of SP-A and SP-D. The mean levels of SP-A, SP-D and KL-6 were not statistically significantly different between the exposed and the non-exposed workers.

The **cross-sectional** study by Nakano et al. (2015) involved 141 workers from 11 factories exposed to indium between 2011 and 2013, who were divided into 5 groups based on their occupation and the type of exposure. In the smelter group, the mean serum indium level of 2.2 µg/l was statistically significantly higher than in the other exposure groups; the highest value of 25.4 µg indium/l serum was also observed in the smelter group. In all other groups, the indium levels in the serum were below 1 µg/l. In the smelter group, the KL-6 level of 322.0 U/ml was also statistically significantly higher than in the other groups. The prevalence of serum indium levels above 3 µg/l in this group was 9.1%, while the

prevalence for KL-6 levels above 500 U/ml was 15.2%. There was a significant correlation between serum indium level and KL-6 ($p < 0.001$) among current employees but not among the previously exposed. The test results for SP-D levels, pulmonary symptoms or lung function did not differ in a statistically significant manner between the groups.

In a 5-year **longitudinal** study, Nakano et al. (2014) examined 240 workers with previous or current indium exposure from 11 factories and 40 non-exposed persons. Serum indium concentrations at baseline were 10.4 µg/l (< 0.1–117) in those exposed, 17.5 µg/l (< 0.1–83.3) in those previously exposed and 0.4 µg/l (< 0.1–1.5) in those not exposed. The geometric mean KL-6 values for these groups were 382.4 U/ml, 373.9 U/ml and 245.8 U/ml, respectively, and the SP-D values were 62.9 ng/ml, 80.7 ng/ml and 42.4 ng/ml, respectively. The mean levels of indium in serum, KL-6 and SP-D of workers exposed to indium at baseline decreased by 29.8%, 27.2% and 27.5%, respectively, during the 5-year follow-up. At the 5-year follow-up, those consistently exposed had a serum indium concentration of 7.3 µg/l (< 0.1–132) and an average KL-6 level of 278.2 U/ml. The previously exposed had a serum indium concentration of 10.6 µg/l (< 0.1–64.4) and an average KL-6 level of 281.7 U/ml. Among those exposed earlier, SP-D was still significantly elevated at 63.0 µg/l (geometric standard deviation (GSD) 2.0) compared with that in controls at 39.9 µg/l (GSD 1.8). In 26.3% of the exposed workers with serum indium levels above 20 µg/l, emphysematous progression was seen in the HRCT. Eighteen of 20 of the workers with emphysematous progression during follow-up were smokers at baseline. For smokers, a trend towards an increasing incidence of emphysematous progression was observed at higher serum indium concentrations ($p = 0.005$). After adjustment for age, mean duration since first indium exposure and smoking history, emphysematous changes were more likely to progress in subjects with serum indium levels above 20 µg/l (odds ratio 10.49; 95% CI: 1.54–71.36).

Choi et al. (2015) analysed data from 50 workers exposed to indium from seven indium-processing factories in Korea. After an exposure period of 44 (2–144) months, the geometric mean serum indium level was 4.8 µg/l (GSD 11.1), the KL-6 level was 817.3 U/ml (GSD 1.7) and the SP-D level was 177.4 ng/ml (GSD 1.8). Higher serum indium and KL-6 levels were associated with interstitial lung changes in the HRCT. Workers with serum indium levels above 3 µg/l had a longer duration of exposure and a higher prevalence of interstitial lung changes detected in the HRCT. The levels of KL-6 and SP-D were statistically significantly higher in the highest serum indium quartile than in the lowest quartile. Statistically significant dose–response relationships existed between serum indium levels and KL-6 and SP-D levels and the prevalence of interstitial lung lesions detected in the HRCT.

Cummings et al. (2014) studied 87 employees of an ITO production plant who had been exposed for a mean of about 4 years. The median indium concentration in serum was 1 µg/l (< 0.03-37). Workers with a serum indium level of > 1 µg/l had significantly more frequently dyspnoea, persistent asthma, changes in spirometry as well as a significantly lowered FEV1 and a lowered vital capacity compared to those exposed to < 1 µg indium/l serum. The values for KL-6 and SP-D were also statistically significantly higher. There were non-significant differences in diffusion capacity. The two study participants who showed early signs of fibrosis on the HRCT had serum indium levels > 1 µg/l.

In another study by Cummings et al. (2016), concentrations of indium in air were determined by stationary and personal sampling (110 samples from 49 workers). Indium exposure was recorded as cumulative exposure. Respirable measured indium concentrations ranged from 0.4 to 108 µg/m^3, and cumulative respirable indium exposure ranged from 0.4 to 923 µg/m^3-years. Higher indium exposures were associated with more dyspnoea, lower spirometric parameters and higher serum biomarkers of lung disease (KL-6 and SP-D), with significant effects starting at an exposure of 22 µg/m^3-years, reached by 46% of participants.

The research group Yang et al. (2021) measured serum indium levels, respiratory symptoms, pulmonary function and serum inflammatory factor levels in twenty ITO processing workers and 15 healthy control persons. The mean duration of indium exposure was 13.87 ± 3.85 months. The mean serum indium concentration in the exposed group was 0.36 ± 0.14 µg/l (0.17–0.57 µg/l), while all values in the control samples were below the limit of detection (< 0.1 µg/l). Compared with the healthy general population, there were no lung changes in the exposed group. In the group exposed to indium, the inflammatory markers G-CSF, IL-4, IL-5, TNF-α and TNF-β were statistically significantly increased, while IL-16 and TIMP-1 were obviously down-regulated. The inflammatory indicators showed a statistically significant correlation with the serum indium levels, with the serum concentrations of the exposed being in the control range of other studies.

Exposure and Effects

Relationship between external and internal exposure

In a cross-sectional study of 69 workers exposed to indium and 69 control persons, Liu et al. (2021) reported both airborne and serum indium concentrations. The indium concentrations (inhalable fraction) in the air of the indium ingot production plant varied from 0.001 to 1.12 mg indium/m^3 (median 0.008 mg indium/m^3). The average level of indium in the ambient air was 0.078 ± 0.065 mg/m^3. In the control group, all measurements were below the quantitation limit of 0.045 µg indium/m^3 air. Accordingly, the serum and urine samples of the indium-exposed individuals showed higher levels than the controls (see Table 1), but no correlation is given in the study. All serum indium concentrations were clearly above the detection limit of 0.053 µg/l serum.

Workers exposed to poorly soluble indium compounds at a factory producing indium ingots in Belgium were studied by Hoet et al. (2012): nine workers exposed for a mean of 5.7 years (1 month to 12 years), five former exposed workers whose last exposure was 3.5 to 14 years ago, and an additional 20 urine and plasma samples from the laboratory of non-exposed workers as controls. Plasma indium concentrations in the 45 samples from the currently exposed were in the range from 0.32–12.61 µg/l (arithmetic mean: 5.41 µg/l) and urine concentrations were in the range from 0.13–8.68 µg/l (arithmetic mean: 1.69 µg/l). Four of the nine currently exposed subjects had plasma concentrations > 3 µg/l, the controls showed values < 0.08 µg/l (plasma) or < 0.05 µg/l (urine). Former (retired) workers showed indium concentrations in urine from < 0.05–3.02 µg/l (arithmetic mean: 0.71 µg/l) and in plasma from < 0.08–4.38 µg/l (arithmetic mean: 1.72 µg/l) (values from table 1 of the publication; in table 3 and the abstract partly deviating data). There was exposure to indium oxide, indium hydroxide, and (to a lesser extent) indium metal and indium chloride. Air concentrations (inhalable fraction) were in the range from 10 to 1030 µg/m^3 with an arithmetic mean of 190 µg/m^3 and a median of 55 µg/m^3. There was no statistically significantly correlation between the concentrations of indium in workplace air and in the biological material.

In workers exposed to indium, or indium oxide, ITO or indium phosphide, no relationship has to date been found between the level of exposure and the level of indium concentration in serum, nor has any relationship been found with indium in urine. Table 1 lists the different studies, some of which are based on different study concepts, some of which used different clinical parameters, but all of which agree that there is no correlation between external and internal exposure.

Tab. 1 Case reports and case-control studies of persons exposed to indium

Exposition (duration), n	Indium in serum [µg/l]	Inflammatory parameters, biomarker pulmonary toxicity, clinical effects	References
ITO (3 years), 1	290	interstitial pneumonia; death due to bilateral pneumothorax; numerous fine particles throughout the lungs	Homma et al. 2003
ITO (4 years), 1	51	FVC%: 93; FEV%: 73; FEV/FVC%: 73; TLC%: 109; DLCO%: 89; KL-6↑; pulmonary fibrosis, emphysema	Homma et al. 2005
ITO (12 years), 1	40	FVC%: 92; FEV%: 82; FEV/FVC%: 78; TLC%: 91; DLCO%: 77; pulmonary fibrosis	Taguchi and Chonan 2006 (cited from Cummings et al. 2012)
ITO (12 years), 1	127	FVC%: 79; FEV%: 76; FEV/FVC%: 84; TLC%: 91; DLCO%: 95; pulmonary fibrosis, emphysema	
ITO (8 years), 1	99	FVC%: 95; FEV%: 52; FEV/FVC%: 49; TLC%: 117; DLCO%: 78; pulmonary fibrosis, emphysema	

Tab. 1 *(continued)*

Exposition (duration), n	Indium in serum [µg/l]	Inflammatory parameters, biomarker pulmonary toxicity, clinical effects	References
ITO (3.3 years[a)]), 78 ITO (4.6 years[b)]), 27 controls, 38[c)]	7.8 ± 4.3[a)] 8.3 ± 4.4[b)] 0.3 ± 2.6	KL-6: 453 ± 1.9 U/ml[a)]; 412 ± 2.2 U/ml[b)]; KL-6 > 500 U/ml (n = 40); exposed persons had statistically significant ↑ in interstitial change in lungs (n = 23); statistically significant difference in TLC % between currently and previously exposed currently exposed: TLC%: 111 ± 12; FRC%: 115 ± 22; FEV/FVC%: 83 ± 7; RV%: 138 ± 31; previously exposed: TLC%: 106 ± 12; FRC%: 110 ± 18; FEV/FVC%: 81 ± 9; RV%: 129 ± 26	Chonan et al. 2007
ITO (4 years), 1 ♂	65	KL-6 ↑; interstitial changes in HRCT, cholesterol clefts FVC%: 74; FEV%: 72; FEV/FVC%: 81; TLC%: 75; DLCO%: 39; pulmonary fibrosis	Nakano et al. 2007 (cited from Cummings et al. 2010)
ITO (10 years), 1 ♂	92	FVC%: 89; FEV%: 89; FEV/FVC%: 82; pulmonary fibrosis, emphysema	Takeuchi 2008 (cited from Cummings et al. 2012)
ITO, 93 controls, 93[c)]	8.25 ± 4.55 0.25 ± 2.64	KL-6: 495.4 U/ml; SP-A: 39.6 ng/ml; SP-D: 85.2 ng/ml: statistically significant increase vs. control group KL-6: 240.1 U/ml; SP-A: 33.8 ng/ml; SP-D: 51.7 ng/ml no statistically significant differences between exposed and unexposed with respect to: spirometry, subjective symptoms, prevalence of interstitial or emphysematous changes, lung HRCT	Hamaguchi et al. 2008
ITO (36.6 ± 26.5 months), 40 ITO (50 ± 16.8 months), 13 ITO (29.3 ± 28.1 months), 27	2.23 ± 3.3 > 3 < 3	statistically significant differences between higher/lower and longer/shorter exposed persons for: KL-6: 365.8 ± 221.8 U/ml and SP-D: 60.4 ± 42.9 U/ml; no statistically significant differences between higher/lower and longer/shorter exposed persons for: VC%: 113.1 ± 14.6; FEV1%: 104.9 ± 12.4; FEV1/VC%: 82.3 ± 7.2 KL-6: 583.3 ± 187.9 U/ml; SP-D: 82.8 ± 50.2 U/ml; VC%: 111.5 ± 12.9; FEV1%: 106.3 ± 12.6; FEV1/VC%: 82.1 ± 8.5 KL-6: 261.0 ± 149.9 U/ml; SP-D: 49.6 ± 35.1 U/ml; VC%: 113.9 ± 15.5; FEV1%: 104.2 ± 12.4; FEV1/VC%: 82.5 ± 6.7	Nogami et al. 2008
Indium[d)], 166 Indium[d)], 68 Indium[d)], 35 Indium[d)], 52 Indium[d)], 50 Indium[d)], 53 controls, 142	< 0.9 1–2.9 3–4.9 5–9.9 10–19.9 > 20	KL-6: 220 U/ml; SP-D: 40.3 ng/ml; SP-A: 28.1 ng/ml KL-6: 255 U/ml; SP-D: 58.9 ng/ml; SP-A: 29.8 ng/ml KL-6: 333 U/ml; SP-D: 54.9 ng/ml; SP-A: 37.5 ng/ml KL-6: 450 U/ml; SP-D: 67.9 ng/ml; SP-A: 43.6 ng/ml KL-6: 511 U/ml; SP-D: 78.8 ng/ml; SP-A: 35.3 ng/ml KL-6: 943 U/ml; SP-D: 121.4 ng/ml; SP-A: 51.3 ng/ml; emphysematous changes: OR 4.42 (95% CI: 0.95–20.60) KL-6: 226 U/ml; SP-D: 49.1 ng/ml; SP-A: 33.1 ng/ml	Nakano et al. 2009
ITO (14 months; > 0.1 mg/m³), 1 ♂ ITO (2 years; > 0.1 mg/m³), 1 ♂		FVC%: 73; FEV%: 82; FEV/FVC%: 90; TLC%: 75; DLCO%: 37; death from respiratory failure due to pulmonary alveolar proteinosis FVC%: 77; FEV%: 83; FEV/FVC%: 87; TLC%: 66; DLCO%: 63; pulmonary alveolar proteinosis	Cummings et al. 2010

Tab. 1 *(continued)*

Exposition (duration), n	Indium in serum [µg/l]	Inflammatory parameters, biomarker pulmonary toxicity, clinical effects	References
ITO (22 months), 1 ♂	152	FVC%: 43; FEV%: 42; FEV/FVC%: 98; DLCO%: 31	Xiao et al. 2010
ITO, 170 controls, 132	1.26 ± 3.09 0.72 ± 2.4	a correlation was found between indium in serum and SP-A and SP-D	Liu et al. 2012
IO (0.010–1.030 mg/m³; AM: 0.190), 9 IO (former), 5 controls, 20	0.32–12.61 (plasma) in urine[e]: 0.13–8.68 < 0.08–4.38 (plasma) in urine[e]: < 0.05–3.02 < 0.08 (plasma) in urine[e]: < 0.05	inhalation of poorly soluble indium compounds can lead to accumulation in the body ⟶ prolonged "endogenous exposure" (from the lungs and other internal organs) parameters indium in urine and indium in plasma remained high even years after discontinuation of exposure ⟶ indication of possible endogenous exposure and persistent risk of lung and systemic diseases even after termination of exposure at the workplace	Hoet et al. 2012
ITO (4.8 (< 1–34) years; 0.1–1 mg/m³), 30 ITO (former, 2.2 (< 1–7.2) years), 27		≥ 5 µg/l: total lung capacity decreased, spirometric restrictions, no correlation between blood test results, medical findings and air concentrations restrictive changes, FEV1↓↓, TLC ↓, DLCO ↓, abnormal thorax X-ray statistically significantly more frequent in employees hired before 2007 ($p < 0.01$). Abnormalities in medical examinations also more frequent in employees with ≥ 5 µg In/l blood, but statistically not significant ($p = 0.07$), no relation between anomalies in medical examinations and indium in the air	Cummings et al. 2013
ITO (24 months), 87	1	at > 1.0 µg indium/l serum: mean serum level of KL-6 and SP-D ↑, dyspnoea ↑, mean FEV1 and FVC levels ↓ spirometric abnormalities were not increased compared with general population; no radiological evidence of pulmonary alveolar proteinosis, pulmonary fibrosis (n = 2), emphysema (n = 4)	Cummings et al. 2014, 2016
ITO (44 (2–144) months), 50 I, 13 II, 12 III, 13 IV, 12	4.8 ± 11.1 ♂: 6.6 ♀: 0.89 < LOD–1.9 2.8–6.3 6.4–24.3 35–125.8	KL-6: 817.3 ± 1.7 U/ml (♂: 885.5 U/ml; ♀: 536.8 U/ml); SP-D: 177.4 ± 1.8 ng/ml (♂: 184.3 ng/ml; ♀: 140.4 ng/ml); cough (n = 18); sputum (n = 19); respiratory sounds (n = 3); dyspnoea on exertion (n = 9) KL-6- and SP-D were statistically significantly higher in group IV compared to group I, trend for differences in the prevalence of interstitial changes in HRCT was statistically significant	Choi et al. 2015

Tab. 1 *(continued)*

Exposition (duration), n	Indium in serum [µg/l]	Inflammatory parameters, biomarker pulmonary toxicity, clinical effects	References
ITO (13.87 months), 40	0.36 ± 0.14	G-CSF: 627.3 ± 417.7 pg/ml (FC: 3.532); IL-4: 73.0 ± 38.9 pg/ml (FC: 3.324); IL-5: 100.6 ± 45.7 pg/ml (FC: 3.247); TNF-α: 2008.1 ± 944.6 pg/ml (FC: 3.298); TNF-β: 501.9 ± 292.43 pg/ml (FC: 4.583); IL-16: 22.2 ± 10.4 pg/ml (FC: 0.254); TIMP-1: 6653.1 ± 767.2 pg/ml (FC: 0.425)	Yang et al. 2021
controls, 40[c)]	< 0.1 µg/l	G-CSF: 177.6 ± 109.6 pg/ml; IL-4: 22.0 ± 14.0 pg/ml; IL-5: 31.0 ± 14.0 pg/ml; TNF-α: 608.9 ± 257.9 pg/ml; TNF-β: 109.5 ± 94.4 pg/ml; IL-16: 87.5 ± 54.5 pg/ml; TIMP-1: 15 639.0 ± 2318.4 pg/ml compared to the control group, G-CSF, IL-4, IL-5, TNF-α and TNF-β were statistically significantly increased in persons exposed to indium, whereas IL-16 and TIMP-1 were statistically significantly downregulated.	

[a)] currently exposed
[b)] previously exposed
[c)] internal
[d)] dusts of several indium compounds
[e)] [µg/l]; values from table 1 of the publication; in table 3 and the abstract partly deviating data
CI: confidence interval; DLCO: diffusing capacity of the lungs for carbon monoxide; FC: fold change; FEV: forced expiratory volume; FRC: functional residual capacity; FVC: forced vital capacity; G-CSF: granulocyte-colony stimulating factor; HRCT: high-resolution computed tomography; IL: interleukin; ITO: indium-tin oxide; KL-6: Krebs von den Lungen 6; OR: odds ratio; RV: residual volume; SP: surfactant protein; TIMP-1: metallopeptidase inhibitor 1; TLC: total lung capacity; TNF: tumour necrosis factor; VC: vital capacity

Selection of the indicators

Indium compounds exert their toxic effects mainly via soluble or solubilised compounds, which are excreted via faeces and kidneys. Studies to date almost exclusively use plasma or serum to detect indium exposure.

Analytical methods

Indium is best determined in serum or urine samples using inductively coupled plasma mass spectrometry (ICP-MS) (Heitland and Köster 2006 a, b). In ICP-MS analysis, indium is determined on the isotope ^{115}In (exact atomic mass: 114.818 u).

Background exposure

Values for background levels of indium in serum, often derived from control samples, are all well below 0.8 µg/l, mostly below 0.3 µg/l, in a few studies with sufficient limits of detection even below 0.1 µg/l. However, individual values can also be just above 1 µg/l. Possible sources of indium exposure of the non-occupationally exposed population are insufficiently known so far. In recent studies, the 95th percentile of the background exposure of the general population in Germany not exposed to indium is below the quantitation limit of the methods used of 0.002 µg indium/l serum (Heitland and Köster 2021).

Evaluation of a BAR

As the 95th percentile of the available data on the background exposure of the general population is below the quantitation limit of the methods used of 0.002 µg indium/l serum and thus the analytics of many laboratories are currently reaching their limits in this very low concentration range,

no biological reference value (BAR) can be derived for indium in serum.

Evaluation of a BLW

The Japan Society for Occupational Health recommended the level of 3 µg indium/l serum as an exposure limit based on biological monitoring to prevent adverse health effects in workers from occupational exposure to indium compounds (Tanaka et al. 2010). From the studies by Cummings et al. (2014) and Liu et al. (2012), the limit for the occurrence of pulmonary effects is more likely to be around 1 µg indium/l serum. Subclinical effects, such as changes in serum parameters, for example KL-6, can be observed starting at 0.3 µg indium/l, so that a biological guidance value (BLW) should be below this concentration. Since analytics in practice reaches its limits in this concentration range,

no BLW is derived for indium.

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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