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Review or Mini-review

The toxicology of indium oxide

Ernst M. Bomhard

REAChChemConsult GmbH, Strehlener Str. 14, D-01069 Dresden, Germany

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ABSTRACT

Indium oxide (In_2O_3) is a technologically important semiconductor essentially used, doped with tin oxide, to form indium tin oxide (ITO). It is poorly soluble in all so far tested physiologic media. After repeated inhalation, In_2O_3 particles accumulate in the lungs. Their mobilization can cause significant systemic exposure over long periods of time. An increasing number of cases of severe lung effects (characterized by pulmonary alveolar proteinosis, emphysema and/or interstitial fibrosis) in workers of the ITO industry warrants a review of the toxicological hazards also of In_2O_3. The database on acute and chronic toxicity/carcinogenicity/genotoxicity/reproductive toxicity as well skin/eye irritation and sensitization is very limited or even lacking. Short-term and subchronic inhalation studies in rats and mice revealed persistent alveolar proteinosis, inflammation and early indicators of fibrosis in the lungs down to concentrations of 1 mg/m^3. Epidemiological and medical surveillance studies, serum/blood indium levels in workers as well as data on the exposure to airborne indium concentrations indicate a need for measures to reduce exposure at In_2O_3 workplaces.

1. Introduction

Indium oxide, (In_2O_3; synonyms: indium trioxide, diindium trioxide, indium sesquioxide, indium(III)oxide; CAS No.: 1312-43-2) apart from several small scale uses, such as some types of batteries, thin film infrared reflectors transparent for visible light, some optical coatings, and some antistatic coatings, is mainly used, doped with tin oxide, to form indium tin oxide (ITO), which has a broad range of applications such as a thin coating on glass or plastics used for touch panels, plasma displays, flat panel displays etc. (NTP, 2009). Its crystalline form has a bixbyite fluorite-type structure with one-quarter of the anions missing (Buchholz et al., 2014; Indium Corporation, 2017).

Occupational exposure to indium containing particles has increased in recent years due to the rising demand for consumer electronics (Choi and An, 2016; Cummings et al., 2013, 2016; NIOSH et al., 2012). Thus, there is a need to assess their hazards and risks, the more because in recent years an increasing number of lung diseases after occupational exposure to indium has been reported in the literature essentially from workers in Korea and Japan, some of which were fatal. One of these cases was a man mainly exposed to In_2O_3 and not to other indium compounds (Takeuchi et al., 2008).

The toxicology of In_2O_3 has been briefly reviewed in the framework of a book chapter covering several indium compounds (Repetto and del Peso, 2012). Since then further data have become available on the toxicology of In_2O_3, but also for other indium compounds which make an update necessary.

In the following, the available data are therefore compiled and critically reviewed.

Data on the toxicity of colloidal hydrated In_2O_3 have not been included because it does not occur as such in the workplace and the environment.

An important role in the toxicology of semiconductors in general seem to play, among others, solubility at biologically relevant conditions i.e. conditions simulating pH values, locally available “solvents” at target sites or cell organelles (lungs, intestine), presence of oxygen etc. For this reason the review starts with a view on this issue.

The journal databases consulted in the course of the review were PubMed, Google and the reference lists of the papers found. The review covers the years 1990–2017.

2. Solubility in vitro

Several papers state that In_2O_3 is insoluble in water and alcohol, soluble in hot organic acids, soluble in hexane and toluene but without giving details of the experimental conditions (ChemicalBook, 2016; Indium Corporation, 2017; Wikipedia, 2017; Zegen Metals&Chemicals Limited, 2017).

In_2O_3 nanoparticles (NPs) at 1 mg/ml were incubated for 1 or 28 days with saline or artificial lysosomal fluid (ALF; pH 5.5) or 0.9% saline. The primary size of the In_2O_3 NPs was 35.8 ± 1.1 nm, while the hydrodynamic size was 212.7 ± 2.2 nm, thus indicating agglomeration. Concentrations of indium in the NP-free supernatant were

E-mail address: bomhard@reach-chemconsult.com.

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measured by inductively coupled mass spectrometry (ICP-MS). Solubility in saline was 1.1% and 3.3%, in ALF 0.6% and 5.5% after one and 28 days, respectively (Jeong et al., 2016).

Quantitative data on its solubility in four types of natural water (rainwater and soil solutions, pH 6.3–7.4) have been reported by Monfort et al. (1988): very small quantities (less than 0.08%) passed into solution during the 11 week test period.

To simulate the dissolution of In_2O_3 particles (specific surface are of $^{<}5\ m^2/g$) that are inhaled and deposited in the conducting airways, a model of airway epithelial-lining fluid referred to as serum ultrafiltrate (SUF; pH 7.4 ± 0.2) and a phagolysosomal simulant fluid (PSF; pH 4.5 ± 0.1) to mimic the acidic environment inside of alveolar macrophage phagolysosomes were evaluated using a static dissolution technique. The dissolution was measured at several time points up to 7 (SUF) and 28 days (PSF). The cumulative total elemental mass dissolved during the study periods was 0.07 ± 0.01% with SUF, and 1.87 ± 0.55% with PSF (Stefaniak et al., 2017). These studies therefore confirm the low solubility of In_2O_3.

3. Acute toxicity

Studies on the acute toxicity of In_2O_3 by the oral, dermal or inhalation route using standard test guidelines are not available.

In the framework of kinetic studies, one rat each was administered a single dose of 300, 500 or 1200 µg Indium as In_2O_3 by intratracheal instillation. Post-treatment observation was up to 14 days. The rat receiving 1200 µg showed weight loss and its lungs contained an albuminous exudate in the alveoli which was unaccompanied by cellular exudate. This was not a common observation in their rats (Morrow et al., 1958).

This is probably the first description of a particle-induced pulmonary alveolar proteinosis (PAP).

Following single intratracheal instillation of 50 mg "pure" In_2O_3 to albino rats 36% had died after 8 months and 70% showed depressed growth compared to controls. Histopathology revealed granular dystrophy of the cells of the liver and kidney. Cloudy swelling of the fibers of the myocardium with focal lymphoid-histiocytic infiltration in the stroma were observed. A large accumulation of dust was discovered in the lymph nodes of the lungs. There was a weak fibrosis of the stroma and hyperplasia of the lymphoid follicles. Regions of significant dust deposition were found in the lungs together with focal desquamative pneumonia, meso- and peribronchitis, proliferation of cell elements of the alveolar membranes, and beginning fibrosis of interstitial tissue (Podosinovskiĭ et al., 1965 cited in Smith et al. 1978).

LD50 values of 479 mg/kg bw (396 mg In/kg)/LD100 of 5005 mg/kg bw (4136 mg In/kg) are reported after ip injection to mice; 1156 (955 mg In/kg) mg/kg bw was the LD100 after ip injection to rats (cited in Smith et al., 1978).

Groups of 5 male Wistar rats were administered single by i.p. injections. The doses ranged from 347 to 1760 mg/kg body weight (bw). Doses of 955 mg/kg or greater were fatal for all animals within 9 days following injection. The doses 347 and 546 mg/kg caused one and two deaths, respectively over the 14-day post exposure period. Marked body weight loss was observed in the surviving rats treated at 546 mg/kg (Downs et al., 1959).

Groups of 3 female Wistar rats were given single i.p. injections at doses of 331, 908 or 1475 mg/kg bw. Levels of 908 and 1475 mg/kg were fatal to all. Deaths occurred between day 9 and 21 following injection. At 331 mg/kg one animal died after day 21. Moderate body weight loss was observed in all groups (Downs et al., 1959).

Acute intravenous toxicity was studied in albino rabbits (one animal per dose) administered single doses of 10–175 mg/kg bw. Deaths occurred within 5 min at dose levels of 90–175 mg/kg. Respiratory difficulties followed by convulsions were observed within 3 min after injection. At 35 to 68 mg/kg delayed toxicity (refused food, body weight loss) was attributed to necrotizing pneumonia and edema. Myelopoiesis, indications of kidney and liver damage were observed in a few rabbits (Downs et al., 1959).

The intravenous treatment of 5 male Wistar rats with a single dose of 30 mg/kg bw (post-treatment observation up to 82 days) revealed pulmonary edema, acute pneumonia and peculiar granular exudate. The body weight was not affected. Rats died or were sacrificed on day 1, 35 (n = 2), 50 and 82 (Downs et al., 1959).

3.1. Special acute studies on lung toxicity

Pulmonary toxicity after single intratracheal instillation of In_2O_3 was investigated in male Sprague-Dawley rats (aerodynamic equivalent particle diameters was $^{<}3$). Dose levels were 1 and 5 mg/rat. Bronchoalveolar lavage fluid (BALF) at 1, 7 and 90 days post treatment revealed significantly, but rather slightly increased cell counts at 5 mg. The cells were mostly polymorphonuclear leukocytes (PMNs) and macrophages. Histopathology at day 90 revealed chronic broncho-interstitial pneumonia, prominent type II pneumocyte hypertrophy and hyperplasia, pleural inflammation and fibrosis, and variable amounts of alveolar exudation consistent with PAP in the lungs of all exposed animals (Badding et al., 2016).

The lung toxicity after single exposure to In_2O_3 NPs was studied using doses of 50, 200, and 600 µg/rat administered to female Wistar rats via pharyngeal aspiration. Lung inflammation was evaluated 1, 3, 14, and 28 days after treatment. Neutrophilic inflammation was observed on day 1 and worsened until day 28, and severe PAP was observed on post-aspiration days 14 and 28 (Jeong et al., 2016).

4. Local effects on skin and mucous membranes

Published studies on local effects on skin and mucous membranes of In_2O_3 using standard test guidelines are not available.

ECHA (no date) classified and labelled In_2O_3 with the following hazard statement codes and phrases: "H315 Causes skin irritation, H319 Causes serious eye irritation and H335 May cause respiratory irritation". No references are provided for these statements.

5. Sensitization

Published studies on skin or respiratory sensitization of In_2O_3 are not available.

6. Subacute/subchronic toxicity

The results of subacute and subchronic inhalation or intratracheal instillation toxicity studies are compiled in Table 1.

The In_2O_3 particle description in these studies were as follows: mean diameter of 1.4 µm with a 90% cumulative diameter of 2.9 µm, MMAD of the aerosols in the exposure chamber 2-week studies: 1.9–2.2 µm (GSD 1.7–1.8); 13-week studies: 2.1–2.3 µm (GSD 1.7) (Nagano et al., 2011a, 2011b); size distribution based on particle mass 0.66 µm (GSD: 2.40) for IO_100 and 1.09 µm (GSD: 1.81) for IO_4000; size distribution based on particle number 0.42 µm (GSD: 1.58) for IO_100 and 0.43 µm (GSD: 1.79) for IO_4000 (Lim et al., 2014); average count median diameter (CMD) 0.182 µm; average calculated mass median diameter 0.63 µm (Leach et al., 1961); primary particle size < 100 nm; secondary particle size 462 ± 236 nm (Noguchi et al., 2016); mean particle diameter 0.14 µm (Tanaka et al., 2010).

In all but one studies mortality and body weights were not affected and treatment-related, clinical signs were not observed. In the 12-week study in Wistar rats with relatively high exposure concentrations, mortality was increased in the exposed animals starting week 9 and 5 in males and females, respectively, and growth was markedly depressed in treated male rats starting week 9. In two animals each histopathology revealed mild interstitial nephritis and focal hepatic necrosis. Various inter-current infections were the usual causes of death complicating

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