INDIUM TIN OXIDE

1. Exposure Data

1.1 Identification

Chem. Abstr. Serv. Reg. No.: 50926-11-9

Chem. Abstr. Serv. Name: indium tin oxide

IUPAC systematic name: indium tin oxide

Other common names: ITO, tin indium oxide, tin doped indium oxide

Molecular formula: In_2O_3; SnO_2

Indium tin oxide (ITO) is a yellow-green solid mixture of indium oxide (In_2O_3, CAS No. 1312-43-2) and stannic (or tin) oxide (SnO_2, CAS No. 18-282-10-5) (Indium Corporation, 2014). The proportion of indium oxide is typically 90% (Hines et al., 2013), but can vary over the range 80–95% (NTP, 2009). As the physicochemical properties of ITO depend on the relative proportions of indium and tin oxides, they are presented below separately for both compounds. As an illustration, the properties for one commercial formula (exact proportion of In_2O_3 not available) are also provided.

Relative molecular mass: 277.64 (In_2O_3); 150.71 (SnO_2) (HSDB, 2017); 264.94 (commercial formula) (Indium Corporation, 2008)

Density: 7.179 g/cm^3 (In_2O_3); 6.95 g/cm^3 (SnO_2) (HSDB, 2017); 7.16 g/cm^3 (commercial formula) (Indium Corporation, 2008)

Melting point: volatilizes at 850 °C (In_2O_3) (Weast, 1970); 1630 °C (SnO_2) (HSDB, 2017); volatilizes at 1910 °C (commercial formula) (Indium Corporation, 2008)

Boiling point: volatilizes at 850 °C (In_2O_3) (Weast, 1970); sublimes at 1800–1900 °C (SnO_2) (HSDB, 2017); sublimes at 982 °C (commercial formula) (Indium Corporation, 2008)

Solubility in water: insoluble (In_2O_3; SnO_2; ITO) (HSDB, 2017)

One manufacturer reported that ITO particle size varies over the range 0.1–1.0 μm depending on grade, with agglomerates varying over the range 7–31 μm (Indium Corporation, 2014).

ITO may contain impurities in small quantities. In the commercial product line of one ITO fabricator, the total concentration of impurities (aluminium, antimony, bismuth, chromium, copper, iron, lead, magnesium, nickel, potassium, sodium, titanium, zinc) does not exceed 100 ppm (UMICORE, 2013).

1.2 Production and use

1.2.1 Production process

ITO can be sintered or unsintered, but typically the occupational exposure is to the sintered form. Sintering uses heat and pressure to combine indium oxide and tin oxide powders to

Table 1.1 Analytical methods for indium in different matrices

Sample matrix	Assay procedure	Limit of detection	Method/reference
Air	ICP-AES	0.015 µg/mL	NIOSH 7303
Plasma	ICP-MS	0.3 µg/L	Cummings et al. (2016)
Serum	ICP-MS	0.1 µg/L	Hamaguchi et al. (2008)
Urine	ICP-MS	0.02 µg/L	Hoet et al. (2012)

AES, atomic emission spectrometry; ICP, inductively coupled plasma; MS, mass spectrometry

form compressed disks called sputtering targets (Cummings et al., 2012a). The process introduces a high density of free electrons and oxygen vacancies in the indium oxide crystal structure, imparting the specific electronic properties of ITO (Lison et al., 2009).

1.2.2 Production volume

ITO production statistics are not publicly available. Indium metal world production was estimated at 755 tonnes for 2015, down from 844 tonnes in 2014 (USGS, 2016). Since ITO production accounts for most (> 70%) of the global indium consumption (NTP, 2009), ITO worldwide production can be estimated for 2015 at more than 529 tonnes. In descending order of importance, China, Republic of Korea, Japan, Canada, and France are the five main indium metal refiners (USGS, 2016).

1.2.3 Use

The main use of ITO is in producing transparent conductive films on glass or plastic panels used in electronic devices and other products, including touch panels, plasma displays, flat panel displays, solar panels, cathode-ray tubes, energy efficient windows, gas sensors, and photovoltaics (NTP, 2009). The sputtering targets (ITO disks or blocks) are bombarded with energetic ions which extract metallic atoms that are deposited as thin films on the desired substrate (Lippens & Muehlfeld, 2012).

1.3 Measurement and analysis

1.3.1 Detection and quantification

Current analytical methods only allow for the quantification of total elemental indium, and cannot quantify ITO. Exposure to humans may occur via inhalation or dermal exposure, and indium is minimally absorbed after ingestion. Inhalation is the primary route for occupational exposures.

Air sampling to determine indium can be performed using the United States National Institute for Occupational Safety and Health (NIOSH) Method 7303 for elements by inductively coupled plasma (ICP). Indium can also be determined in serum, plasma, or urine samples (Table 1.1) by ICP mass spectrometry.

1.3.2 Biological markers

Indium levels in plasma and serum samples are highly correlated (Harvey et al., 2016). Indium air concentrations and biological levels (in urine and plasma) of workers at an indium ingot production plant showed no correlation however (Hoet et al., 2012), but the number of subjects was small (9 current and 5 former workers, and 20 controls). A study in an ITO production facility reported that plasma indium had a stronger relationship with cumulative (r = 0.77) than current exposure (r = 0.54) (based on personal sampling of respirable indium). This finding was driven by workers with a longer tenure (≥ 1.9 years) (Cummings et al., 2016). Hoet et al. (2012) found that neither plasma nor urine levels increased

significantly during the day (before vs after shift) or during the week. Biological levels in former workers (3.5–14 years since last exposure) were still higher than in unexposed controls (Hoet et al., 2012). Nakano et al. (2009) also reported that former indium-exposed workers (2–200 months since last exposure) had similar serum indium levels to currently exposed workers and significantly higher levels than unexposed workers (Nakano et al., 2009). Biological levels of indium therefore appear to better reflect chronic exposures rather than recent, due to accumulation in the body.

1.4 Occurrence and exposure

1.4.1 Environmental occurrence

ITO does not occur naturally; however, elemental indium is present naturally as a small percentage (estimated range, 50–250 ppb) in the Earth's crust. Indium is produced mainly from zinc ore processing, but is also found in small amounts in iron, lead, and copper ores (Alfantazi & Moskalyk, 2003; Enghag, 2007). Elemental indium has been characterized in seawater at 0.2–0.7 ppb, in air at 43 ng/m^3, and in rainwater at 0.59 µg/L (IARC, 2006; Enghag, 2007; Schwarz-Schampera, 2014).

1.4.2 Exposure to the general population

The average daily human intake of indium has been estimated as 8–10 µg/day from dietary sources, which is considered a minimal dietary exposure (Scansetti, 1992).

1.4.3 Occupational exposure

Exposure to ITO primarily occurs in occupational settings where ITO is produced or processed, or where elemental indium is recycled and recovered from ITO; these exposures are summarized in Table 1.2.

No data are available to estimate the number of workers exposed to ITO.

During 2009–2011, NIOSH contacted indium-using companies in the USA to characterize where and how indium is used. ITO was reported to be used primarily as a transparent conductive oxide on polymer substrates, or in the manufacture of sputter targets or photovoltaic cells (Hines et al., 2013). At a company that sputters indium-containing thin films onto polymer, NIOSH task-based sampling data (2010) were combined with company sampling data (2004); air indium concentration varied over the range 0.018–9.8 mg/m^3 by job task and ventilation controls. Combining task-based NIOSH and company sampling data at two photovoltaic companies, indium in air varied over the range 0.072–5.4 mg/m^3 by job task and reported exposure controls (Hines et al., 2013).

ITO became an occupational exposure of interest in the early 2000s, when several case reports related to indium exposure appeared in the literature. In a series of three case reports from Japan, three workers involved in wet-surface grinding of ITO all presented with interstitial pulmonary disease and serum indium concentrations of 40, 99, and 127 µg/L (Taguchi & Chonan, 2006). At another ITO processing facility in Japan, a worker with a serum indium concentration of 290 µg/L died from pulmonary fibrosis (Homma et al. 2003). These serum indium measurements were at the upper end of the exposure distribution reported in other workplaces for multiple workers (Tanaka et al., 2010a; Omae et al., 2011).

Several studies have used biological monitoring to assess indium exposures in workplaces using ITO (see Table 1.2). Liu et al. (2012) measured serum in exposed workers at four ITO manufacturing plants in Taiwan, China, and unexposed administrative controls at the same plants. The exposed workers had a geometric mean serum indium concentration of 1.26 µg/L (maximum 18.4 µg/L), whereas the geometric

Table 1.2 Measurement of indium in facilities producing or processing indium tin oxide

Reference	Location, collection date	Occupation	Sampling matrix; *n* (duration)	Exposure level	Exposure range	Comments
Homma et al. (2003)	Japan, 2000	ITO processing	Serum; *n* = 1	290 µg/L		Case report of ITO worker who presented for pulmonary dysfunction
Homma et al. (2005)	Japan, 2002	Transparent conductive film manufacturing	Serum; *n* = 1	51 µg/L		Case report of ITO worker who presented for pulmonary dysfunction
Taguchi and Chonan (2006)	Japan, NR	ITO manufacturing plant	Serum; *n* = 3	40, 127, and 99 µg/L		Three case reports of interstitial pneumonia, reported by Tanaka et al. (2010a); originally reported by Taguchi and Chonan (2006)
Cummings et al. (2010)	USA, 2005	ITO-producing facility	Lung; *n* = 1	29.3 µg/g lung tissue	NR	Case report of ITO worker who presented for pulmonary dysfunction
Liu et al. (2012)	Taiwan, China NR	ITO manufacturing plants	Serum; *n* = 170	1.26 µg/L (geometric mean)	Maximum, 18.4 µg/L	
		Administrative controls at same ITO plant as exposed	Serum; *n* = 132	0.72 µg/L (geometric mean)	NR	
Chonan et al. (2007)	Japan, 2002	ITO manufacturing plant, formerly exposed	Serum; *n* = 27	8.3 µg/L (geometric mean)	NR	
		ITO manufacturing plant, currently exposed	Serum; *n* = 78	7.8 µg/L (geometric mean)	NR	
		Administrative controls at same ITO plant as exposed	Serum; *n* = 38	0.3 µg/L (geometric mean)	NR	
		ITO manufacturing plant	Total dust; *n* = 8 locations (≥ 10 min)	10–50 µg/m^3 (geometric mean)	Maximum, 360 µg/m^3	Range of geometric means found at the eight stationary locations (it is unclear how many samples were taken at each location); sampling occurred for at least 10 min using a low-volume sampling pump

Table 1.2 (continued)

Reference	Location, collection date	Occupation	Sampling matrix; *n* (duration)	Exposure level	Exposure range	Comments
Hamaguchi et al. (2008)	Japan, 2003–2004	ITO manufacturing or recycling plants	Serum; *n* = 93	8.25 µg/L (geometric mean)	< 0.1–116.9 µg/L	
		Administrative controls	Serum; *n* = 93	0.25 µg/L (geometric mean)	< 0.1–1.3 µg/L	
Nakano et al. (2009)		ITO factories and research laboratory, currently exposed	Serum; *n* = 465	8.35 µg/L (arithmetic mean)	< 0.1–116.9 µg/L	Includes data from Chonan et al. (2007) and Hamaguchi et al. (2008)
		ITO factories and research laboratory, formerly exposed	Serum; *n* = 127	9.63 µg/L (arithmetic mean)	< 0.1–126.8 µg/L	
		Administrative controls at same ITO factories as exposed	Serum; *n* = 169	0.56 µg/L (arithmetic mean)	< 0.1–3.0 µg/L	
Cummings et al. (2012a)	USA, 2002–2010	ITO production	Blood; *n* = 42	3.8 µg/L (median)	< 5–63 µg/L	*n* = 21 subjects had a blood In concentration above the LOD; median blood In concentration was 12 µg/L with a range of 5.1–63 µg/L
			Total dust; *n* = 11 (full shift)	NR	9–136 µg/m^3	Total dust area samples taken at four locations in the plant: In_2O_3 production area, ITO tile-making area, grinding area, and reclaim area using open-faced 37 mm cassettes Respirable In of 2–42 µg/m^3 measured at the same locations using cyclones with 37 mm cassettes
Harvey et al. (2016)	USA, 2014	ITO production facility	Plasma; *n* = 50	3.48 µg/L (arithmetic mean)	NR	
			Serum; *n* = 50	3.90 µg/L (arithmetic mean)	NR	
			Blood; *n* = 50	4.66 µg/L (arithmetic mean)	NR	

Table 1.2 (continued)

Reference	Location, collection date	Occupation	Sampling matrix; *n* (duration)	Exposure level	Exposure range	Comments
Nogami et al. (2008)	Japan, NR	In recycling facility	Serum; *n* = 40	2.23 µg/L (arithmetic mean)	NR	Research conducted by Nogami et al. (2008), published in Japanese; reported by Omae et al. (2011)
Cummings et al. (2016)	USA, 2012	ITO facility workers	Respirable air; personal; *n* = 110 (full shift)	NR	0.4–108.4 µg/m^3	Respirable samples collected using the GK2.69 cyclone
Choi et al. (2013)	Republic of Korea, 2012	ITO manufacturing and reclaiming factories	Serum; *n* = 34	10.9 µg/L (geometric mean)	< LOD–125.8 µg/L	
Iwasawa et al. (2017)	Japan, 2013–2014	ITO processing plant	Respirable air; personal; NR (251–483 min)	NR	0.004–24.0 µg/m^3	Samples standardized to 8 h TWA; respirable sample collected using GS-3 respirable dust cyclone or TR sampler (PM4 NWPS-254)
			Serum; *n* = 64 (251–483 min)	NR	< 0.1–8.5 µg/L	
Hoet et al. (2012)	Belgium, NR	In ingot production plant	Inhalable air; personal; NR	175 µg/m^3 (arithmetic mean)	10–1030 µg/m^3	Plant where workers are mainly exposed to In_2O_3 but also to $In(OH)_3$, In metal, and $InCl_3$; personal air samples collected using IOM samplers for inhalable fraction

Table 1.2 (continued)

Reference	Location, collection date	Occupation	Sampling matrix; *n* (duration)	Exposure level	Exposure range	Comments
Liu et al. (2016)	Japan, 2010–2012	ITO sputter target manufacturing plant	Respirable air; personal; $n = 54$ (average 365 min)	NR	2–3 μg/m^3	Personal respirable samples collected using a cyclone; geometric means presented for the respirable samples by year
			Total dust; personal; $n = 40$ (average 365 min)	NR	21–34 μg/m^3	Personal total dust samples collected using a closed-face sampling cassette; geometric means presented for the total dust samples by year
			Outside PAPR; personal; $n = 15$ (average 85 min)	53 μg/m^3 (arithmetic mean)	24–105 μg/m^3	15 samples were collected inside and outside a PAPR simultaneously
			Inside PAPR; personal; $n = 15$ (average 85 min)	3 μg/m^3 (arithmetic mean)	2–8 μg/m^3	

In, indium; $InCl_3$, indium chloride; In_2O_3, indium oxide; $In(OH)_3$, indium hydroxide; IOM, Institute of Occupational Medicine; ITO, indium tin oxide; LOD, limit of detection; NR, not reported; PAPR, powered air-purifying respirator; TWA, time-weighted average

mean for the unexposed workers was 0.72 µg/L (Liu et al., 2012). Exposed workers at an ITO manufacturing plant in Japan had a geometric mean serum indium concentration of 7.8 µg/L, while unexposed administrative controls from the same plant had a geometric mean serum indium concentration of 0.3 µg/L (Chonan et al., 2007). Another study from Japan compared serum indium in currently exposed, formerly exposed, and unexposed workers at ITO factories and a research laboratory using ITO. Those currently exposed had a mean serum indium concentration of 8.35 µg/L (range, < limit of detection (LOD) to 116.9 µg/L), those formerly exposed had a mean serum indium concentration of 9.63 µg/L (range, < LOD–126.8 µg/L), and those unexposed to ITO had a mean serum indium concentration of 0.56 µg/L (range, < LOD–3.0 µg/L) (Nakano et al., 2009).

Despite these studies measuring serum indium (or, less commonly, blood or plasma) in workplaces using ITO, and studies measuring airborne indium exposures in workplaces using ITO, few studies have compared biological markers of indium exposure with indium exposure in workplace air. Cummings et al. (2016) compared respirable and cumulative airborne exposure to indium with plasma indium concentration in 87 ITO facility workers. Table 1.3 summarizes personal respirable indium air samples by department in the ITO facility; all samples taken were personal samples with the exception of one area sample. Personal respirable indium (110 samples from 49 workers) measured over a full work shift varied over the range 0.4–796.6 µg/m^3; the highest exposure levels were for workers in the reclaim area, followed by those in the ITO department, grinders, and in research and development. The background level in the administrative department was 0.4 µg/m^3. Cumulative exposures to indium ranged from 0.4 to 923 µg-year/m^3, based on individual job tasks and time in each job. Median plasma for the 87 workers was reported as 1 µg/L. The respirable concentrations of indium reported by Cummings et al. (2016) were comparable to previous reports of indium in air (in total dust, and inhalable and respirable fractions) in occupational settings using ITO (Chonan et al., 2007; Cummings et al., 2012a, 2016).

Liu et al. (2016) measured indium in air both inside and outside of powered air-purifying respirators (PAPRs) on 15 ITO sputter target manufacturing workers and found that the use of a PAPR reduced exposures to indium by an average of 93.4%. These workers also showed a decrease in geometric mean serum indium and urine indium 10 months after implementation of PAPRs in the workplace, with geometric mean serum decreasing from 5.28 to 4.05 µg/L, and geometric mean urine indium decreasing from 0.81 to 0.74 µg/g creatinine (Liu et al. 2016).

1.5 Regulations and guidelines

No specific limit values for occupational exposure to ITO exist. Almost 20 countries do have 8-hour time-weighted average (TWA) limit values for exposure to indium and compounds (as In) which are set across the board at 0.1 mg/m^3. Corresponding short-term limit values do exist in a few countries and range from 0.2 to 0.3 mg/m^3 (GESTIS, 2017). The Japan Society for Occupational Health (JSOH) recommended an occupational exposure limit based on the biological monitoring of indium in serum of 3 µg/L in 2007 (Iwasawa et al., 2017).

2. Cancer in Humans

No data were available to the Working Group.

3. Cancer in Experimental Animals

See Table 3.1

Table 1.3 Personal respirable indium exposure levels by department at a facility producing indium tin oxide

Department	*n*	Mean indium exposure (μg/m³)	Range of indium exposure (μg/m³)
ITO	25	81.9	9.9–518.3
Planar bond	5	9.1	3.2–17.6
Planar grind	8	27.2	4.6–148.4
Reclaim	12	108.4	4.8–796.6
Refinery	6	26.3	10.9–40.9
Rotary bond	9	3.7	0.7–6.4
Rotary grind	4	39.4	20.9–59.3
Engineering	9	4.9	1.7–23.2
Maintenance and facilities	8	8.6	2.2–16.0
Forming	8	5.7	1.3–12.4
Quality control laboratory	6	3.5	1.9–5.4
Research and development	8	35.5	2.1–111.1
Shipping and receiving	2	1.9	1.7–2.1
Administrative (area sample)	1	0.4	NR

ITO, indium tin oxide; NR, not reported
Adapted from: Cummings et al. (2016), with permission of John Wiley & Sons

3.1 Mouse

3.1.1 Inhalation

In the study by Nagano et al. (2011a), groups of 50 male and 50 female B6C3F$_1$/Crlj mice (age, 6 weeks) were exposed to sintered ITO (90.06% In_2O_3 + 9.74% SnO_2, median aerodynamic particle diameter of 1.8–2.4 μm) or clean air via whole-body inhalation (6 hours per day, 5 days per week) under good laboratory practice (GLP) conditions. Mice were killed after 104 weeks of exposure. The ITO exposure concentrations were 0 (air control), 0.01, 0.03, or 0.1 mg/m³. In females, there was a significant positive trend in the incidence of adenoma of the lung and of adenoma or carcinoma (combined) of the lung at week 104 after exposure to ITO. The incidences of bronchioloalveolar adenoma in female mice were 1/50, 0/50, 2/50, and 4/47, and the incidences of bronchioloalveolar adenoma or carcinoma (combined) were 3/50, 0/50, 3/50, and 7/47 at the 0, 0.01, 0.03, and 0.1 mg/m³ ITO exposure concentrations, respectively. There was no significant increase in the incidence of bronchiolo-alveolar carcinoma in female mice or in the incidence of any type of lung tumours in male mice after ITO exposure. [The Working Group noted that study strengths were the 2-year GLP bioassay for chronic toxicity, use of a physiologically relevant exposure route, testing of sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio, and use of both sexes.]

3.2 Rat

3.2.1 Inhalation

In the study by Nagano et al. (2011a), groups of 50 male and 50 female F344 rats/DuCrlCrlj (age, 6 weeks) were exposed to sintered ITO (90.06% In_2O_3 + 9.74% SnO_2, median aerodynamic particle diameter of 1.8–2.4 μm) or clean air via whole-body inhalation (6 hours per day, 5 days per week) under GLP conditions. Rats were killed after 104 weeks of exposure. The ITO exposure concentrations were 0 (air control), 0.01, 0.03, or 0.1 mg/m³. For the highest tested

Table 3.1 Studies of carcinogenicity with indium tin oxide in experimental animals

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of lung tumours	Significance	Comments
Full carcinogenicity Mouse, B6C3F$_1$ (M) 6 wk 104 wk Nagano et al. (2011a)	Inhalation (whole-body exposure) ITO, 99.8% Clean air 0, 0.01, 0.03, 0.1 mg/m^3 6 h/d, 5 d/wk 50, 50, 50, 50 31, 33, 28, 30	Bronchioloalveolar adenoma 5/50, 4/50, 5/50, 5/50 Bronchioloalveolar carcinoma 7/50, 1/50, 4/50, 5/50 Combined all lung tumours 12/50, 5/50, 9/50, 10/50	 NS NS NS	Principal strengths: full 2-year GLP long-term study; physiological exposure route (inhalation); used sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio; used both sexes All lung tumours were bronchioloalveolar adenomas or carcinomas
Full carcinogenicity Mouse, B6C3F$_1$ (F) 6 wk 104 wk Nagano et al. (2011a)	Inhalation (whole-body exposure) ITO, 99.8% Clean air 0, 0.01, 0.03, 0.1 mg/m^3 6 h/d, 5 d/wk 50, 50, 50, 50 38, 32, 34, 34	Bronchioloalveolar adenoma 1/50*, 0/50, 2/50, 4/47 Bronchioloalveolar carcinoma 2/50, 0/50, 1/50, 3/47 Combined all lung tumours 3/50**, 0/50, 3/50, 7/47	 Trend test, *P < 0.05 (Peto test) NS Trend test, **P < 0.01 (Peto test)	
Full carcinogenicity Rat, F344 (M) 6 wk 104 wk Nagano et al. (2011a)	Inhalation (whole-body exposure) ITO, 99.8% Clean air 0, 0.01, 0.03, 0.1 mg/m^3 6 h/d, 5 d/wk for 26 wk (0.1 mg/m^3) or 104 wk 50, 50, 50, 50 39, 38, 41, 40	Bronchioloalveolar adenoma 3/49*, 5/50, 10/50*, 12/50* Bronchioloalveolar carcinoma 0/49*, 4/50, 5/50*, 5/50*	 Trend test, *P < 0.05 (Peto test) Pairwise, *P < 0.05 (Fisher test) Trend test, *P < 0.05 (Peto test) Pairwise, *P < 0.05 (Fisher test)	Principal strengths: full 2-year GLP long-term study; physiological exposure route (inhalation); used sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio; used both sexes Historical control incidence of adenosquamous carcinoma at the laboratory, 0/2399

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of lung tumours	Significance	Comments
Nagano et al. (2011a) (cont.)		Adenosquamous carcinoma 0/49, 1/50, 0/50, 0/50 Combined malignant lung tumours 0/49*, 5/50*, 5/50*, 5/50* Combined all lung tumours 3/49**, 10/50*, 15/50**, 16/50**	NS Trend test, *$P < 0.05$ (Peto test) Pairwise, *$P < 0.05$ (Fisher test) Trend test, **$P < 0.01$ (Peto test) Pairwise, **$P < 0.01$ (Fisher test)	
Full carcinogenicity Rat, F344 (F) 6 wk 104 wk Nagano et al. (2011a)	Inhalation (whole-body exposure) ITO, 99.8% Clean air 0, 0.01, 0.03, 0.1 mg/m^3 6 h/d, 5 d/wk for 26 wk (0.1 mg/m^3) or 104 wk 50, 50, 50, 50 41, 42, 41, 43	Bronchioloalveolar adenoma 1/50, 5/49, 6/50, 7/49* Bronchioloalveolar carcinoma 0/50**, 1/49, 9/50**, 5/49* Adenosquamous carcinoma 0/50, 1/49, 0/50, 0/49 Squamous cell carcinoma 0/50, 1/49, 0/50, 1/49 Combined malignant lung tumours 0/50**, 3/49, 9/50**, 6/49*	Trend test, *$P < 0.05$ (Peto test) Pairwise, *$P < 0.05$ (Fisher test) Trend test, *$P < 0.05$ and **$P < 0.01$ (Peto test) Pairwise, *$P < 0.05$ and **$P < 0.01$ (Fisher test) NS NS Trend test, *$P < 0.05$ and **$P < 0.01$ (Peto test) Pairwise, *$P < 0.05$ and **$P < 0.01$ (Fisher test)	Principal strengths: full 2-year GLP chronic study; physiological exposure route (inhalation); used sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio; used both sexes Historical control incidence of: adenosquamous carcinoma at the laboratory, 1/2197; and squamous cell carcinoma at the laboratory, 0/2197

Table 3.1 (continued)

Study design Species, strain (sex) Age at start Duration Reference	Route Agent tested, purity Vehicle Dose(s) No. of animals at start No. of surviving animals	Incidence of lung tumours	Significance	Comments
Nagano et al. (2011a) (cont.)		Combined all lung tumours 1/50**, 8/49*, 14/50**, 13/49**	Trend test, $^{**}P < 0.01$ (Peto test) Pairwise, $^{**}P < 0.01$ (Fisher test)	
Full carcinogenicity Hamster, Syrian golden (M) 8 wk Up to 86 wk Tanaka et al. (2010b)	Intratracheal instillation ITO, 74.4% In and 7.8% Sn by weight Distilled water 0, 0, 6, 6 mg/kg bw 2×/wk for 8 wk 7–8, 6–8, 8, 7–8 7, 6, 8, 7	Bronchioloalveolar adenoma 0/7 (wk 48), 0/6 (wk 86), 1/8 (wk 48), 2/7 (wk 86)	NS	Principal limitations: only one sex; small number of animals per group; NR if ITO 90:10 (In_2O_3:SnO_2); NR if ITO sintered; non-physiological exposure route

bw, body weight; d, day; F, female; In, indium; GLP, good laboratory practice; ITO, indium tin oxide; M, male; NR, not reported; NS, not significant; Sn, tin; wk, week(s)

concentration (0.1 mg/m^3), rats were exposed to ITO for 26 weeks followed by air for the remaining 78 weeks. At week 104, the incidences of preneoplastic lesions (bronchioloalveolar hyperplasia) were significantly increased in male and female exposed rats. The incidences of bronchioloalveolar adenoma in male rats were 3/49, 5/50, 10/50, and 12/50, and in female rats 1/50, 5/49, 6/50, and 7/49 at the 0, 0.01, 0.03, and 0.1 mg/m^3 ITO exposure concentrations, respectively. The increases in the incidence of bronchioloalveolar adenoma with ITO at 0.03 and 0.1 mg/m^3 were significant in male rats (with a significant positive trend) and significant at 0.1 mg/m^3 ITO in female rats. The incidences of bronchioloalveolar carcinoma in male rats were 0/49, 4/50, 5/50, and 5/50, and in female rats 0/50, 1/49, 9/50, and 5/49 at the 0, 0.01, 0.03, and 0.1 mg/m^3 ITO exposure concentrations, respectively. Bronchioloalveolar carcinomas of the observed in exposed rats were often accompanied by proliferative fibrous connective tissue, not commonly seen in spontaneous bronchioloalveolar carcinomas observed in control F344 rats. The increases in the incidences of bronchioloalveolar carcinoma were significant in male and female rats at ITO concentrations of 0.03 and 0.1 mg/m^3, respectively, with a significant positive trend. In one male and one female rat given ITO at a concentration of 0.01 mg/m^3, there was an adenosquamous carcinoma of the lung. At ITO doses of 0.01 and 0.1 mg/m^3, there was a squamous cell carcinoma of the lung in one female rat. There was a significant increase in the incidence of combined malignant lung tumours (with a significant positive trend) for all groups of exposed male rats (0/49, 5/50, 5/50, and 5/50 at the 0, 0.01, 0.03, and 0.1 mg/m^3 ITO exposure concentrations, respectively) and for the 0.03 mg/m^3 and 0.1 mg/m^3 groups of ITO-exposed female rats. There was a significant increase in the incidence of combined (all) lung tumours (with a significant positive trend) for all groups of exposed male and female rats. [The Working Group noted that male and female rats exposed only for 26 weeks to the high dose had a significant increase in the incidence of bronchioloalveolar carcinoma. In addition, males at the lowest dose had a significant increase in the incidence of combined malignant lung tumours. Study strengths were noted as: the 2-year GLP chronic bioassay, use of a physiologically relevant exposure route, testing of sintered ITO at a 90:10 (In_2O_3:SnO_2) ratio, and use of both sexes.]

3.3 Hamster

3.3.1 Intratracheal instillation

In a study conducted by Tanaka et al. (2010b), male Syrian golden hamsters (age, 8 weeks) were exposed to ITO (74.4% indium and 7.8% tin by weight; mean particle diameter, 0.95 ± 2.42 μm) or indium oxide (In_2O_3 > 99.99%; mean particle diameter, 0.14 μm), or exposed as vehicle controls (sterile distilled water; n = 40) via intratracheal instillation twice per week for 8 weeks. The initial ITO treatment groups (3 mg/kg body weight (bw), n = 40; or 6 mg/kg bw, n = 40) and indium oxide treatment groups (2.7 mg/kg bw, n = 23; or 5.4 mg/kg bw, n = 23) were selected so that equimolar indium was given for each (4.5 mg/kg bw indium for the highest exposure level, 2.2 mg/kg bw indium for the lowest). Groups of 6–8 vehicle control, indium oxide, and ITO-exposed hamsters were killed at 48 or 86 weeks. Body weights were decreased in the ITO treatment group at 6 mg/kg bw (vs controls). Relative lung weights were increased for all exposed groups (vs controls). Severe inflammation (including infiltration of alveolar macrophages and neutrophils) and bronchioloalveolar cell hyperplasia were observed at week 86 for both ITO exposure levels. For the 6 mg/kg bw ITO and both indium oxide groups, there were low incidences of localized alveolar or bronchiolar cell proliferating lesions. Bronchioloalveolar adenomas were observed in the 6 mg/kg bw ITO-exposed groups at 48 weeks (1/8) and 86

weeks (2/7); the combined incidence (3/15) was low and not statistically significant. No bronchioloalveolar adenomas were observed in 48-week and 86-week vehicle controls (0/7 and 0/6, respectively) or in hamsters exposed to indium oxide (0/8 and 0/8 in the 48-week groups; week 86 was not assessed). [The Working Group noted that this 'chronic' study actually involved subchronic exposure only with an extended observation phase. All deaths due to cannibalization or emaciation were excluded from the evaluation. Limitations were noted as: use of a non-physiological 'bolus' exposure route, testing of only one sex, lack of information regarding whether the ITO was sintered and at a 90:10 (In_2O_3:SnO_2) ratio (most relevant to occupational exposures), the low number of animals per group for tumour evaluation, and the combination of groups from different time points for the purpose of statistical analyses. The Working Group concluded this was an uninformative study.]

4. Mechanistic and Other Relevant Data

4.1 Toxicokinetic data

Data on metabolism and excretion of ITO are sparse. Elemental indium (In) has been measured in exposed humans and in experimental systems, and a few rodent studies have shown that inhaled or intratracheally instilled ITO is slowly dissolved, systemically available, widely distributed, and slowly eliminated over a period of years. The distribution of indium to tissues suggests indium dissolution from ITO particles. The precise form of indium in tissues was not reported in any of the studies, and the excretion of indium was not well characterized.

4.1.1 Humans

In a cross-sectional study, 93 workers from 2 ITO manufacturing plants and 2 ITO recycling plants where ITO (> 50%) was the major indium species in the dust had an overall serum indium geometric mean concentration of 8.25 µg/L (maximum, 116.9 µg/L) compared with 0.25 µg/L in 93 unexposed workers (Hamaguchi et al., 2008). [The Working Group noted possible confounding by exposure to other indium compounds in dusts, including indium oxide (approximately 40%) and indium (approximately 10%).]

In 170 workers from 2 ITO-producing plants in Taiwan, China, the mean indium serum concentration (1.26 µg/L) was significantly higher than that in 132 administrators who served as controls (Liu et al., 2012). [The Working Group noted that it was not specified whether those workers who showed serum concentrations above 3 µg/L, the occupational exposure limit set by JSOH, were in the exposed group.]

Several case reports of workers at the same Japanese worksite provided data on serum indium concentrations. The indium serum concentration of a 27-year-old Japanese man engaged in wet-surface polishing of ITO targets, 3 years after stopping work at the facility and 1 year before his death, was 290 µg/L compared with a mean of 0.1 µg/L reported for 377 healthy workers (Homma et al., 2003). A 30-year-old man exposed to ITO aerosols who was diagnosed with pulmonary fibrosis, most likely due to ITO exposure [as reported in the study], had a serum indium concentration of 51 µg/L (compared with a normal value of < 0.1 µg/L) (Homma et al., 2005). Another 3 additional workers (out of 115 ITO workers) had high serum indium concentrations (40, 127, and 99 µg/L) (Taguchi & Chonan, 2006; Omae et al., 2011). In another report of 108 men at the same Japanese worksite, the range of serum indium concentrations was observed to increase with increasing number of years of exposure (Chonan et al., 2007).

4.1.2 Experimental systems

Several inhalation studies have analysed ITO deposition and biodistribution in rodents. In male Sprague-Dawley rats exposed to ITO particles (average size, < 50 nm) via nose-only inhalation for 4 weeks (~1 mg/m^3 of indium by mass concentration), indium was mainly deposited in the lungs, eliminated slowly, and distributed, in descending order of concentration, to the spleen, liver, and brain (Lim et al., 2014). Indium also distributed to the blood and serum. [The Working Group noted that measurements of indium were only reported for lungs; for other tissues, precise concentrations of indium were not reported.] In male and female F344 rats exposed to ITO aerosols for 6 hours per day, 5 days per week for 2 weeks (0, 0.1, 1, 10, or 100 mg/m^3) and 13 weeks (0, 0.1, or 1 mg/m^3), ITO particles deposited in the lung and, to a lesser extent, in the bronchus-associated lymphoid tissue, mediastinal lymph nodes, and nasal-associated lymphoid tissue (Nagano et al., 2011b). All ITO doses had a mass concentration of indium of 75–80%. [The Working Group noted that the number of mice with particles, but not concentrations of the particles, was reported.] Indium contents in blood and lung were elevated in a dose-dependent manner in both the 2-week and 13-week studies. The group exposed to 0.1 mg/m^3 over 13 weeks were then exposed to clean air for 26 weeks; indium contents in the lung were found to be reduced by 60% and blood contents were elevated approximately 1.3-fold compared with concentrations at 13 weeks of exposure (Nagano et al., 2011b).

In male Sprague-Dawley (Hla:(SD) CVF) rats, particles from both indium oxide and sintered ITO (SITO) induced time-dependent increases in plasma indium concentrations, with SITO particles causing a much greater increase (85.3 µg/L) compared with indium oxide (< 2.0 µg/L) (Badding et al., 2016). Plasma indium from ventilation dust installations peaked after 1 week of exposure, inducing concentrations (93.5 µg/L) similar to those of SITO at 90 days of exposure. The rats were given intratracheal instillations of 3 different particle samples (In_2O_3 and SITO at doses of 1 and 5 mg per rat, and ventilation dust at doses of 0.5 and 1.0 mg per rat) collected at various production stages throughout an ITO facility for 90 days (Badding et al., 2016).

In F344/DuCrlCrlj rats and B6C3F$_1$/Crlj mice of both sexes, ITO particles were deposited mainly in the lung [half-life not calculated] and, to a lesser extent, in the mediastinal lymph node, nasal-associated lymphoid tissue, and bronchus-associated lymphoid tissue (Nagano et al., 2011c). Rats (0, 0.01, or 0.03 mg/m^3 ITO) and mice (0, 0.01, 0.03, or 0.1 mg/m^3) were exposed by aerosol for 6 hours per day, 5 days per week, for 104 weeks. Male and female rats were also exposed to 0.1 mg/m^3 ITO for 26 weeks followed by exposure to clean air for 78 weeks. In the rats exposed to 0.1 mg/m^3, indium was also detected in the spleen, kidney, liver, bone marrow, ovary, pancreas, testis, epididymis, and blood. Blood contents of indium in rats exposed to 0.01 and 0.03 mg/m^3 ITO increased in a dose-dependent manner. In mice, indium was only detected in those given the 0.1 mg/m^3 dose (both sexes) and in females given the 0.03 mg/m^3 dose. In general, blood indium content was higher in female mice than in males (Nagano et al., 2011c).

In male and female B6C3F$_1$ mice exposed to ITO aerosols for 6 hours per day, 5 days per week for 2 weeks (0, 0.1, 1, 10, or 100 mg/m^3) or 13 weeks (0, 0.1, or 1.0 mg/m^3), indium was deposited in the lungs and, to a lesser extent, the mediastinal lymph nodes (Nagano et al., 2011a). Mean indium contents in the lungs of groups exposed to doses of 0.1 and 1 mg/m^3 (13-week exposure) were 11.5 and 77.4 µg/g for male mice and 7.8 and 74.9 µg/g for female mice, respectively. Pooled blood contents of indium (1 mg/m^3 group) were 0.58 and 0.90 µg/L for male and female mice, respectively (Nagano et al., 2011a).

In male Syrian golden hamsters, indium concentrations gradually increased from the end

of exposure at 8 weeks to 78 weeks after intratracheal instillations of 3 or 6 mg/kg of ITO particles containing indium at 2.2 or 4.5 mg/kg twice per week for 8 weeks (Tanaka et al., 2010b, 2015). Concentrations reached 0.237 and 0.436 μg/L in the serum, 8.37 and 14.42 μg/L in the liver, 9.362 and 17.773 μg/L in the kidney, and 2.91 and 5.682 μg/L in the spleen at the end of the observation period, for the groups at 3 and 6 mg/kg, respectively. Indium content in the lungs slowly decreased, with elimination half-lives of approximately 142 and 124 weeks for the 3 and 6 mg/kg doses, respectively (Tanaka et al., 2010b, 2015).

4.2 Mechanisms of carcinogenesis

The sections that follow summarize the evidence for the "key characteristics" of carcinogens (Smith et al., 2016). Sections 4.2.1–4.2.4 address whether: ITO induces chronic inflammation; is genotoxic; alters cell proliferation, cell death, and nutrient supply; and induces oxidative stress. There were insufficient data for the evaluation of other key characteristics of human carcinogens.

4.2.1 Chronic inflammation

(a) Humans

In the case reports of ITO-exposed workers with interstitial lung disease, also called indium lung disease (Homma et al., 2003, 2005; Cummings et al., 2010, 2012b), increased accumulation of inflammatory cells including alveolar macrophages, lymphocytes, and plasma cells in the airways/lung was described.

In a study in vitro, SITO particles were readily taken up by human bronchial epithelial (BEAS-2B) cells and induced proinflammatory signalling via nuclear factor-kappa B (NFκB) activation within 3 hours of exposure. ITO also induced production of the proinflammatory cytokines IL-6 and IL-8 by BEAS-2B cells at 24 hours, but did not induce nod-like receptor protein 3 (NLRP3) inflammasome activation (Badding et al., 2015).

In a study in vitro by Tabei et al. (2016), sample B ('indium release ITO') induced increased proinflammatory IL-8 expression by A549 cells. Treatment of activated human blood derived monocytes (THP-1 cells) with ITO nanoparticles (NPs) induced increased production of TNFα and IL-1β (Naji et al., 2016).

(b) Experimental systems in vivo

(i) Rats

In the chronic study by Nagano et al. (2011a), as previously described in Section 3.2.1, extensive inflammation was observed in the lungs of ITO-exposed F344 rats (both sexes) at weeks 26 and 104.

Lung inflammation was also observed in male and female F344 rats in an experiment in which exposure was to ITO at 0.1 mg/m^3 for 13 weeks (6 hours per day and 5 days per week) and then to air for 26 weeks (Nagano et al., 2011a). When F344 rats were exposed to SITO (0.1, 1, 10, or 100 mg/m^3), indium oxide, or clean air via whole-body inhalation for 6 hours per day and 5 days per week, and killed after 2 weeks of exposure, lung inflammation was observed in SITO-exposed rats of both sexes, as was increased infiltration of alveolar macrophages (Nagano et al., 2011a).

In male Sprague-Dawley rats exposed via intratracheal instillation to SITO, indium oxide, or vehicle and killed 1, 7, or 90 days later (Badding et al., 2016), total cells (including macrophages and neutrophils) and proinflammatory cytokines (TNFα, IL-6 and IL-1β) were increased in bronchioloalveolar lavage fluid (BALF), predominantly for ITO. The doses tested were 1 or 5 mg per rat.

Lung inflammation was observed in female Wistar-Han rats 60 days after a single dose of SITO (2 mg or 20 mg) via oropharyngeal aspiration, compared with exposures to non-sintered ITO (non-SITO) (2 mg or 20 mg), indium oxide

(1.8 mg or 18 mg), stannic oxide (0.2 mg or 2 mg), or saline vehicle (Lison et al., 2009). Three days after exposure, acute airway/lung inflammation was evident in SITO-treated rats compared with the other treatment groups, including non-SITO and indium oxide. Acute alveolitis and inflammatory nodules were also observed in the lung, and total cells were increased in the BALF, 3 days after exposure to SITO (Lison et al., 2009).

Total cells (including neutrophils) in BALF were significantly increased for all groups (vs air-only control) of male Sprague-Dawley rats exposed to indium oxide (< 4000 nm or < 100 nm) or ITO 50 (< 50 nm) containing 1 mg/m^3 indium via nose-only inhalation for 6 hours per day, 5 days per week for 4 weeks (some rats were held an additional 4 weeks without further treatment) (Lim et al., 2014). The greatest increases were for rats exposed to ITO 50 compared with the other exposure groups at both time points. Perivascular inflammation (including alveolar macrophages) in the lung was also present to some extent in all indium-exposed groups, but was highest for the rats exposed to ITO 50 at both time points (Lim et al., 2014).

(ii) Mice

In the chronic study by Nagano et al. (2011a), as previously described in Section 3.1.1, extensive inflammation was observed in the lungs of ITO-exposed B6C3F$_1$ male and female mice at week 104.

Lung inflammation was also observed 2 or 13 weeks after exposure to SITO in male and female B6C3F$_1$ mice (Nagano et al., 2011a). Mice were exposed to SITO, indium oxide, or clean air via whole-body inhalation, as described in Section 3.2.1 for rats (Nagano et al., 2011b).

Treatment of Balb/c mice with ITO NPs via intraperitoneal injection induced NLRP3 inflammasome-dependent peritonitis with increased recruitment of neutrophils and production of proinflammatory IL-1β (Naji et al., 2016).

(iii) Hamsters

In the long-term study by Tanaka et al. (2010b) described in Section 3.3.1, severe inflammation (including infiltration of alveolar macrophages and neutrophils) was observed in the lungs of ITO-exposed hamsters at week 86 for both ITO exposure levels (3 and 6 mg/kg bw).

Mild inflammation (including accumulation of alveolar macrophages and neutrophils) was observed in the lungs of ITO-treated male Syrian golden hamsters (Tanaka et al., 2002). The hamsters were exposed to ITO at 6 mg/kg bw (or In at 4.5 mg/kg bw) or vehicle control via intratracheal instillation once per week for 16 weeks (16 doses total), and animals were killed the day after the final dose.

(c) Experimental systems in vitro

SITO particles were readily taken up by mouse macrophages (RAW 264.7 cells) and induced proinflammatory signalling via NFκB activation within 3 hours of exposure (Badding et al., 2015). ITO induced production of the proinflammatory cytokines TNFα and IL-1β by RAW 264.7 cells at 24 hours, as well as increased caspase-1 activity. Activation of caspase-1, together with increased IL-1β production, was indicative of NLRP3 inflammasome activation within ITO-treated RAW 264.7 cells (Badding et al., 2015). Treatment of mouse peritoneal macrophages or alveolar macrophages (MH-S cells) with ITO NPs induced increased production of TNFα and/or IL-1β (Naji et al., 2016).

4.2.2 Genetic and related effects

(a) Humans

Indium concentrations were increased in the serum of ITO-exposed workers who also exhibited increased DNA damage in whole blood as measured by comet assay in a cross-sectional study (Liu et al., 2012). A reduction in exposure was found to decrease the DNA damage by comet assay (Liu et al., 2016).

ITO-exposed workers exhibited increased urinary and leukocyte 8-hydroxy-2′-deoxyguanosine (8-OHdG) (Liu et al., 2012; Liou et al., 2016, 2017) as well as increased exhaled breath condensate 8-isoprostane (Liou et al., 2017), biomarkers of oxidative damage to DNA.

In an assay for micronucleus formation in human peripheral lymphocytes in vitro, ITO NPs increased the frequency of micronuclei (Akyıl et al., 2016).

ITO NPs were readily taken up by the human lung adenocarcinoma cell line A549 within 24 hours of exposure and induced DNA damage at 24–72 hours by comet assay (Alkahtane, 2015; Tabei et al., 2015). In the study by Tabei et al. (2016), A549 cells were exposed to two types of SITO NPs: sample A (720 μg/mL In_2O_3 + 70 μg/mL SnO_2) or sample B (200 μg/mL In_2O_3 + 15 μg/mL SnO_2). Based on transmission electron microscopy and measurements of intracellular indium concentrations by ICP-MS at 24 hours, sample B was taken up better (into lysosomal structures) than sample A. Sample B was solubilized within the cells, resulting in indium release extracellularly (as measured by ICP-MS at 24 hours), and was therefore called "indium release ITO"; sample A was solubilized within the cells, resulting in tin release, and therefore called "tin release ITO". The highest concentration of genotoxicity (as measured by comet assay) was induced in A549 cells by sample B (indium release ITO) at 24 hours (Tabei et al., 2016).

(b) Experimental systems

Positive results in the micronucleus assay were observed in rat type II pneumocytes collected 3 days after treatment with SITO via oropharyngeal aspiration at a dose of 2 mg per rat (Lison et al., 2009).

ITO NPs were not mutagenic in an Ames test using *Salmonella typhimurium* strains TA98 and TA100 (Akyıl et al., 2016), but gave positive results in comet assay using *Allium cepa* root cells (Ciğerci et al., 2015).

4.2.3 Altered cell proliferation, cell death, or nutrient supply

(a) Humans

No data in exposed humans were available to the Working Group.

In vitro, ITO particles were cytotoxic to BEAS-2B cells based on an assay for 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) viability at 24 and 48 hours (Badding et al., 2014). In studies using A549 cells, ITO NPs induced cytotoxicity at 48 hours with increased caspase activity and the formation of condensed chromosomal bodies indicative of apoptosis (Alkahtane, 2015). In the study by Tabei et al. (2016), exposure to sample B (indium release ITO) also decreased A549 cell viability (by WST-1 assay) and cell proliferation/colony formation. Treatment of activated human blood derived monocytes (THP-1 cells) with ITO NPs induced cell death (Naji et al., 2016).

(b) Experimental systems

Alveolar epithelial hyperplasia was observed in the lungs of ITO-treated rats and mice (Nagano et al., 2011a, b; Lim et al., 2014; Badding et al., 2016) as well as in hamsters (Tanaka et al., 2002, 2010b).

In rat alveolar macrophages (NR8383 cells), but not rat lung epithelial cells, treatment with SITO for 24 hours resulted in the phagocytic uptake of particles and cytotoxicity via measurements of increased lactate dehydrogenase (LDH) release (Lison et al., 2009). In studies by Gwinn et al. (2013, 2015), non-SITO and SITO particles were readily phagocytosed by RAW 264.7 cells. Particle solubilization, cytotoxicity (based on assays for MTT viability and LDH release), and the extracellular release of indium (μg/L; as measured by atomic absorption spectroscopy) were seen at 24 hours. In addition, ITO particles were phagocytosed by mouse alveolar epithelial (LA-4) cells but did not induce cytotoxicity or indium release at 24 hours, although

particle-induced alveolar epithelial cell cytotoxicity was increased at 48 hours. Cytochalasin D (an inhibitor of phagocytosis) or bafilomycin A1 (an inhibitor of phagolysosomal acidification) blocked particle-induced cytotoxicity and indium release in RAW 264.7 cells, indicating that solubilization of ITO particles, via the phagolysosomal pathway, is linked to particle-induced cytotoxicity (Gwinn et al. 2013, 2015). ITO particles were cytotoxic to RAW 264.7 cells, based on an assay for MTT viability at 24 and 48 hours (Badding et al., 2014). ITO also induced caspase 3/7 activation in RAW 264.7 cells, indicative of apoptosis. Treatment of mouse peritoneal macrophages or alveolar macrophages (MH-S cells) with ITO NPs induced cell death (Naji et al., 2016).

4.2.4 Oxidative stress

(a) Humans

The antioxidants glutathione peroxidase and superoxide dismutase were decreased in the study of ITO-exposed workers noted above (see Section 4.2.2) (Liou et al., 2016, 2017). Use of PAPRs in an interventional study reduced serum indium concentrations in ITO-exposed workers as well as biomarkers of oxidative stress, including lipid peroxidation (based on MDA assay) and glutathione *S*-transferase in plasma as well as 8-OHdG in urine (Liu et al., 2016).

In several in vitro studies, ITO NPs induced increased intracellular production of reactive oxygen species (ROS) and expression of haem oxygenase 1 mRNA, most noticeably at 72 hours, in A549 cells (Tabei et al., 2015). Additionally, ITO NPs decreased glutathione and increased lipid hydroperoxide, superoxide activity, and ROS production by A549 cells (Alkahtane, 2015). In the study by Tabei et al. (2016), increased MTIIA and haem oxygenase 1 mRNA concentrations, as well as increased intracellular ROS production, were induced at 24 hours in A549 cells by sample B (indium release ITO).

(b) Experimental systems

No data from experimental systems in vivo were available to the Working Group.

In vitro, treatment of zebrafish liver cells with ITO NPs for 24 hours increased production of ROS and expression of oxidative stress-related genes including mt2 (Brun et al., 2014). Using a cell-free system, SITO was shown to generate ROS (Lison et al., 2009).

4.3 Cancer susceptibility

No data were available to the Working Group.

4.4 Other adverse effects

4.4.1 Humans

The characteristics of indium lung disease in individuals exposed occupationally to ITO included impaired pulmonary function associated with alveolar proteinosis, fibrosis, and emphysematous changes (Bomhard, 2016). Serum indium concentrations, as well as biomarkers of interstitial lung injury such as Krebs von den Lungen-6 (KL-6) glycoprotein, surfactant protein (SP)-A, SP-D, LDH, and Clara cell (CC16) protein, were also increased in the serum of ITO-exposed workers (Bomhard, 2016).

In two workers (a non-smoker aged 49 years and a smoker aged 39 years) exposed to airborne ITO dust at an ITO-producing facility in the USA, pulmonary alveolar proteinosis and indium in lung tissue specimens were seen (Cummings et al., 2010). A case of pulmonary alveolar proteinosis was also reported in a Chinese male aged 29 years working with an ITO spraying process; his indium serum concentration was 151.8 µg/L (Xiao et al., 2010).

4.4.2 Experimental systems

In male and female ITO-treated rats at 104 weeks, increased relative lung weights, hyperplasia of the alveolar epithelium, alveolar wall fibrosis, infiltration of alveolar macrophages, pleural wall thickening, alveolar proteinosis, and inflammation in the lung were observed (Nagano et al., 2011a, b; Lim et al., 2014; Badding et al., 2016; Section 3). Granulomas were also described in these studies in the bronchus-associated lymphoid tissue (BALT) and lung-draining mediastinal lymph nodes (MLNs). LDH activity and total protein concentrations, which are indicative of airway damage, were increased in the BALF of ITO-treated rats (Lison et al., 2009; Lim et al., 2014).

In ITO-treated mice, alveolar wall fibrosis, pleural thickening, and alveolar proteinosis were observed in the lungs (Nagano et al., 2011a, c). BALT and MLN hyperplasia, as well as extramedullary haematopoiesis in the spleen, were also described in these studies. Immune activation based on increased lymphocyte proliferation (T-cell mediated responses) in a local lymph node assay was induced in female Balb/c mice exposed to non-SITO NPs dermally or via intradermal injection (Brock et al., 2014).

In ITO-treated hamsters, alveolar wall and pleural thickening as well as expansion of the alveolar spaces were observed in the lungs (Tanaka et al., 2002, 2010b). Testicular toxicity in the form of epithelial vacuolization of the seminiferous tubules was described in male Syrian Golden hamsters treated with ITO with 6 mg/kg bw via intratracheal instillation once per week for 16 weeks (Omura et al., 2002).

5. Summary of Data Reported

5.1 Exposure data

Indium tin oxide (ITO) is a mixture of indium oxide (In_2O_3) and stannic oxide (SnO_2), not naturally occurring. ITO is a low production volume chemical, the main use of which is in producing transparent conductive films on glass or plastic panels used in electronic devices and other products. Exposure to ITO occurs primarily in occupational settings where ITO is produced or processed, or where elemental indium is recycled and recovered from ITO. Current analytical methods can only quantify total elemental indium, not ITO. A serum indium concentration was reported at 290 µg/L in a case of pulmonary dysfunction in an ITO worker. Mean serum indium concentrations of up to 11 µg/L have been reported among exposed workers.

5.2 Human carcinogenicity data

No data were available to the Working Group.

5.3 Animal carcinogenicity data

One well-conducted inhalation study in male and female mice and one well-conducted inhalation study in male and female rats were performed under good laboratory conditions. One intratracheal instillation study in male hamsters was conducted.

ITO exposure significantly increased the incidences of bronchioloalveolar adenoma, bronchioloalveolar carcinoma, combined malignant lung tumours, and combined (all) lung tumours in male and female rats, often with a significant positive trend. In female mice, there was a significant positive trend in the incidence of bronchioloalveolar adenoma and bronchioloalveolar adenoma or carcinoma (combined), but there was no significant increase in the incidences

of bronchioloalveolar adenoma, carcinoma, or adenoma or carcinoma (combined) by pairwise comparison. There was no significant increase in tumour incidence in male mice.

The intratracheal study in hamsters was uninformative.

5.4 Mechanistic and other relevant data

Elemental indium (In) has been measured in exposed humans, in rodents, and in vitro after ITO exposure, but the metabolism of ITO has not been well characterized. A few rodent studies showed that inhaled or intratracheally instilled ITO is slowly dissolved, made systemically available, widely distributed, and slowly eliminated over a period of years. ITO deposited in the lung can be distributed to blood, serum, and multiple tissues (liver, spleen, and brain), and is excreted in urine. The distribution of indium to tissues suggests dissolution from ITO particles. Exposure to ITO can result in substantial levels of indium in biofluids (e.g. blood, urine, and serum), and particle solubilization has been demonstrated in vitro. The excretion of indium has not been well characterized.

With respect to the key characteristics of human carcinogens, adequate data were available to evaluate whether ITO induces chronic inflammation, is genotoxic, alters cell proliferation or death, and induces oxidative stress. Only a few studies from exposed humans were available.

The evidence that ITO induces chronic inflammation is *strong*, based on findings in experimental systems. In the few case reports available, increased inflammation in the airways and lung was observed in ITO-exposed workers with interstitial lung disease. In the 2-year ITO study in both sexes of rats and mice, as well as in a long-term study in hamsters, chronic lung inflammation was seen. Numerous subchronic studies in multiple strains of rats and mice also showed inflammatory responses. Several in vitro studies in human and mouse cells showed that ITO induced proinflammatory signalling and cytokine production.

The evidence that ITO is genotoxic is *moderate*. Two studies in exposed humans from the same investigators showed increased DNA damage in blood cells and increased urinary 8-OHdG. An independent study in exposed humans showed that ITO increased 8-OHdG in leukocytes and in urine. One in vivo study in rats showed increased frequency of micronuclei in type II pneumocytes after exposure to sintered ITO by oropharyngeal aspiration. In several in vitro studies, ITO increased the frequency of micronuclei in human peripheral lymphocytes and induced DNA damage in human lung adenocarcinoma cells and in plant root cells. Ames assay results were negative.

The evidence that ITO alters cell proliferation or death is *moderate*. No data in exposed humans were available. Alveolar epithelial hyperplasia was reported in exposed rats, mice, and hamsters. ITO induced cell death in multiple studies using human or rodent cells in vitro.

The evidence that ITO induces oxidative stress is *weak*. There were a few studies in exposed humans, showing that ITO increased 8-isoprostane in exhaled breath, increased lipid peroxidation in plasma, and decreased plasma antioxidant enzymes. No in vivo studies were available in experimental systems. In vitro, ITO increased biomarkers of oxidative stress in human A549 cells.

There were no data on cancer susceptibility.

In exposed humans, ITO induced interstitial lung disease associated with alveolar proteinosis and fibrosis. Similar effects were seen in exposed rats, mice, and hamsters.

6. Evaluation

6.1 Cancer in humans

There is *inadequate evidence* in humans for the carcinogenicity of indium tin oxide.

6.2 Cancer in experimental animals

There is *sufficient evidence* in experimental animals for the carcinogenicity of indium tin oxide.

6.3 Overall evaluation

Indium tin oxide is *possibly carcinogenic to humans (Group 2B)*.

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