1 **Solubility of Indium-Tin Oxide in simulated lung and gastric**

2 **fluids: Pathways for human intake**

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Abstract

From being a metal with very limited natural distribution, indium (In) has recently become disseminated throughout the human society. Little is know of how In compounds behave in the natural environment, but recent medical studies link exposure to In compounds to elevated risk of respiratory disorders. Animal tests suggest that exposure may lead to more widespread damage in the body, notably the liver, kidneys and spleen. In this paper, we investigate the solubility of the most widely used In compound, indium-tin oxide (ITO) in simulated lung and gastric fluids in order to better understand the potential pathways for metals to be introduced into the bloodstream. Our results show significant potential for release of In and tin (Sn) in the deep parts of the lungs (artificial lysosomal fluid) and digestive tract, while the solubility in the upper parts of the lungs (the respiratory tract or tracheobronchial tree) is very low.

Our study confirms that ITO is likely to remain as solid particles in the upper parts of the lungs, but that particles are likely to slowly dissolve in the deep lungs. Considering the prolonged residence time of inhaled particles in the deep lung, this environment is likely to provide the major route for uptake of In and Sn from inhaled ITO nano- and microparticles. Although dissolution through digestion may also lead to some uptake, the much shorter residence time is likely to lead to much lower risk of uptake.

1. Introduction

There is increasing evidence to suggest that indium (In) compounds may be harmful to human health, yet the potential transfer mechanisms into the human body are very poorly understood. While in vivo tests on mice and rats have shown that In-phosphide, In-arsenide In-trichloride and In-acetate have toxic and carcinogenic effects (Chapin et al., 1995; Oda, 1997; Tanaka, 2004, Lee et al., 2016), the most widely used compound, indium-tin oxide (ITO), was until recently considered to be comparably inert (Fowler et al., 2009). However, studies by Homma et al. (2003) and Cummings et al. (2010, 2016) linked health problems and fatalities among factory workers to their exposure to ITO. Indeed, mounting evidence from recent research suggests that exposure to ITO can be directly linked to lung disorders, such as pulmonary alveolar proteinosis, pulmonary fibrosis, emphysema, and pneumothoraces (Chonan et al., 2007; Lison et al., 2009; Nakano et al., 2009; Omae et al., 2011, Cummings et al., 2012, 2016; Badding et al., 2015, 2016). Experiments on rats by Nagano et al. (2011) furthermore indicate that exposure to ITO may linked to increased risk of malignant lung tumors.

Despite the very low solubility of ITO, Chonan et al. (2007) and Hamaguchi et al. (2008) found elevated concentrations of In in serum from current and former workers exposed to ITO at a factory in Japan. These studies suggest that the ITO does not remain entirely inert upon intake, but that In is released to circulate more widely within the human body. Very little research has been carried out to document any wider health effects, but Omura et al. (2002) suggested that exposure to ITO may lead to testicular toxicity in hamsters. Bomhard (2016), however, suggested that damage to the male sexual organs may be a secondary effect from the lung damage. In more general terms, Smith et al. (1978) and Blazka (1998) suggest that chronic exposure to In may lead to weight loss and damage to the

76 liver, kidneys and spleen, and it is likely that once In from ITO enters the bloodstream, it may

77 have similar effects as ionic or colloidal In compounds (cf., Smith et al., 1978, Blazka, 1998).

78   In this study, we report the results of in vitro experiments to examine the dissolution

79 behavior of ITO in simulated lung and gastric fluids and discuss the potential transfer

80 mechanisms for In and associated tin (Sn) into the human body.

81

82 **2.   Background**

83   Indium is a metal that belongs to group 13 of the periodic table along with boron,

84 aluminum, gallium and thallium. The principal oxidation state is trivalent and the effective

85 ionic radius for In^{3+} in 8-fold coordination is 0.092 nm (Shannon, 1976), which is

86 intermediate between scandium and the lanthanides. The metal is predominantly found in

87 sulfide minerals that are unstable under oxidizing conditions at the Earth's surface.

88 Consequently it is likely to be released during acid mine drainage. Tin in contrast occurs

89 principally in the form of cassiterite (SnO_2) which is very stable in the environment and tends

90 to be residual after weathering.

91   Indium is very rare in the natural environment and has historically had very little use

92 in society. Tin in contrast, although also naturally rare, has a history of human exploitation

93 that dates back millennia, and it's environmental and health effects are much better

94 constrained. However, through the distribution of mobile electronic devices, flat-screen

95 televisions and computer displays, In has over the last decade appeared extensively in the

96 human environment (White and Hemond, 2012). As a consequence, the global potential for

97 exposure has increased dramatically, and concerns about environmental and health issues

98 must be considered with some urgency.

99   The most widespread use of In is in sintered indium-tin oxide (ITO), which is applied

100 as a conductive coating on flat-screen liquid crystal displays in mobile electronic devices,

computer monitors and televisions. Indium is also used in lead-free solders, light-emitting

diodes, and copper-indium-gallium-selenide (CIGS) photovoltaic panels. As flat screen

displays are now almost completely replacing cathode-ray televisions and computer monitors,

and mobile electronic devices are becoming more widespread, ITO can be expected to start

appearing in the domestic waste stream in significant quantities. Flat screen displays contain

on average 234 mg In per square meter (Böni and Widmer, 2011); the average lifetime of a

mobile electronic device is estimated to less than 5 years, while the lifetime of a domestic flat

panel television or computer monitor is estimated to 9 years (USEPA, 2011). While a

significant proportion of computer monitors are recycled (38%), televisions and mobile

telephones have very poor recycling statistics (17% and 8% respectively, USEPA, 2011) and

mostly end up in the household waste. The global end-of-life recycling rate for In was

estimated to be less than 1% in 2011 (Graedel et al., 2011).

During the lifetime of a flat-screen display, the ITO is not exposed, and it therefore

does not pose immediate risk to general consumers. Apart from during manufacture, the main

risks for release of ITO particles would be during recycling and disposal of the devices,

where ITO coated glass is typically mechanically abraded before In is recovered by chemical

leaching (Zeng et al, 2015; Zhang et al., 2015).

The biological residence time of ITO particles in the body is a significant parameter to

consider in relation to intake. Only a small fraction of insoluble particles are likely to be

retained within the upper respiratory tract or tracheobronchial tree (Patrick and Stirling, 1977;

Watson and Brain, 1979; Gore and Patrick, 1982). However, as particles are introduced to the

deep lung environment (the bronchioles and alveoli), they are likely to accumulate over

extensive periods of time. Radford and Martell (1977) estimated that the residence time for

insoluble particles in bronchial tissue derived from cigarette smoke amounted to 3 to 5

months. The digestive system, in contrast, has a much shorter transit time, with solid particles

126 being excreted typically after one to three days (Daugherty and Mrsny, 1999). Morrow et al.

127 (1957) determined the biological half-life of In_2O_3 in rats (administrated orally or by

128 inhalation) to be in the order of 9-10 days, however, a recent study by Amata et al. (2015)

129 suggests that the actual residence times of In in humans may be in the order of 8 years.

130   The United States recommended exposure limits in air are 0.1 mg/m^3 In and 2 mg/m^3

131 inorganic Sn (NIOSH, 1981), which with an inhalation rate of 20-25 m^3/day for an average

132 weight adult male (Brochu et al., 2006) would equate to a maximum accumulation in the

133 lungs of 0.67-0.83 mg In for an eight hour working day (probably as high as 1 mg In for

134 obese adults). With less than 10 wt% SnO_2, the inhalation of Sn from ITO is much less of an

135 issue. The regulated exposure limit for In in Japan is much more restrictive at 0.0003 mg/m^3

136 (MHLW, 2010). The United States minimal risk level for oral intake of inorganic Sn is 0.3

137 mg/kg/day (ATSDR, 2016) while no safe level appears to have been identified for In.

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139 **3.   Materials and Methods**

140   For this study, we used ITO powder (<44 μm, 325 mesh, ≥ 99.99% purity trace metal

141 basis, Sigma Aldrich 494682-25G, CAS 50926-11-9:d 1.2) listed to have a composition of 90

142 wt% In_2O_3 and 10 wt% SnO_2. The powder is similar in composition and particle size to the

143 material used to produce ITO sputtering targets (Falk, 2012). The production of sputtering

144 targets involves the densification of the ITO particles under pressure and at high temperature

145 to form a granular solid with or without binders or additives (Falk, 2012). During sputtering,

146 nanoparticles are released through heating of the target to deposit as a thin conductive coating

147 on the substrate (Tuna et al., 2010). The coating consists of nanoparticles that are typically

148 tens of nanometers across (Kim et al., 2000).

149   The powder was investigated by powder X-ray diffraction (XRD) and electron-probe

150 microanalysis (EPMA) at Camborne School of Mines, University of Exeter, to establish the

151 structure and variability and particularly to confirm that the material had been sintered. The

152 XRD was conducted on a Siemens D5000 equipped with the Bruker Topas software using the

153 JCPDS database (ICDD, 2004). The EPMA analysis was carried out on the JEOL JXA-8200

154 using a 30 nA electron beam accelerated to 15 kV and wavelength-dispersive X-ray

155 spectrometers. Results were quantified with tin metal, indium-arsenide, and wollastonite

156 standards using the CITZAF routine (Armstrong, 1995).

157 Dissolution experiments were carried out in screw-capped polypropylene beakers

158 (SCP Science DigiTUBES, product 010-500-261). Samples were prepared in triplicate with a

159 procedural blank for each set. Experiments were designed to simulate key environments that

160 are considered to be significant routes for particle intake. A set of control experiments were

161 carried out with ITO in deionised water (purified with an Elga/Veolia Purelab Flex system).

162 The gastric environment was simulated with the physiologically based extraction test

163 (PBET) solution of Ruby et al. (1996), however our experiments were conducted without

164 suspended particles or gas flow. Tests were conducted for up to four hours, exceeding the

165 maximum residence time of food in a child's stomach (Ruby et al., 1996). The pH of the

166 solution was adjusted to 4 using concentrated HCl, as this value was considered intermediate

167 between the conditions of fasting and full. A separate test was carried out with trypsin in

168 deionised water at neutral pH, as a simplistic way of testing if digestive enzymes may

169 facilitate further dissolution.

170 The lung environment was explored using the formulations of Colombo et al. (2008):

171 Gamble's solution is used to simulate the conditions as ITO particles are inhaled (in the upper

172 respiratory tract and tracheobronchial tree), while artificial lysosomal fluid (ALF) is

173 considered to replicate the more acidic conditions in the deep lung (bronchioles and alveoli).

174 Stock solutions (Table 1) were prepared as specified by Ruby et al. (1996) and

175 Colombo et al. (2008). Particular care was taken to add the components of Gamble's solution

176   in the correct order to avoid salt precipitation. All plastic ware was soaked in dilute HNO_3,

177   rinsed in deionised water and oven dried prior to use in the experiments.

178   Experiments were carried out in triplicate using separate beakers (rather than aliquots

179   from a single beaker) with a procedural blank for each set of three samples. For each

180   experiment, 50 mg of ITO powder was weighed into the polypropylene beakers and 10 ml of

181   the required stock solution added (time zero) using an Eppendorf Research Plus® pipette

182   with non sterile, single use pipette tips. After addition of the fluids, the experiments were

183   sealed, gently swirled to ensure maximum wetting of the ITO powder without leaving ITO

184   particles on the beaker walls, and transferred to an oven at 37ºC. The gastric experiments

185   were carried out with residence times of up to 4 hours, while the lung experiments extended

186   to 480 hours. A separate experiment was conducted to test the influence of enzymes on the

187   digestion, for this experiment, 150 mg ITO and 50 mg trypsin (from porcine pancreas, Sigma,

188   T4799-5G, Lot# 110M7362V) was weighed into the beakers and 25ml of de-ionised water

189   added. The beakers were swirled to ensure complete wetting of the ITO powder and trypsin

190   and placed in an oven at 37ºC. These experiments were carried out with residence times of up

191   to >200 hours.

192   At the termination of each experiment, three sample beakers and one blank were

193   collected and the solution immediately vacuum filtered through a single-use 0.45 µm Teflon

194   membrane (SCP Science DigiFILTER, product 010-500-070) and stored at room temperature

195   prior to analysis. None of the plastic ware was re-used.

196   The samples were analyzed for ^{28}Si, ^{39}K, ^{56}Fe, ^{115}In and ^{118}Sn by the Agilent 7700x

197   quadrupole inductively-coupled mass spectrometer (ICP-MS) at Camborne School of Mines,

198   University of Exeter using ^{45}Sc as internal standard. Samples were introduced in undiluted

199   form using an Agilent ASX-520 autosampler. The ICP-MS was fitted with a Peltier cooled

200   Scott type spray chamber and an inert PTFE sample introduction system. Indium and Sn were

201   measured with helium as a collision cell gas to suppress polyatomic mass interferences. The

202   CeO^+/Ce^+ was 0.136% and the Ce^{2+}/Ce^+ was 1.372%.

203   The interference of ^{115}Sn (0.34% of the natural abundance of Sn) on ^{115}In was

204   negligible (< 0.14 ppb) at the measured concentrations. ^{28}Si and ^{56}Fe were used as monitors

205   of potential contamination through handling of reagents and beakers, the Si was

206   systematically below 2µg/g and Fe below 0.5µg/g. The internal standard recovery was 96.6 ±

207   14.2 %) except for Gamble's solution (117.6 ± 9.0 %). The instrument was calibrated with

208   1.6, 8, 40, 200, 1000 and 2000 µg/kg solutions, while a 40 µg/kg standard solutions was

209   tested after every 12 analyses to monitor instrument drift. After each analysis, the sample

210   introduction system was flushed with deionized water followed by dilute HNO_3 and a further

211   wash with deionized water. No carryover was observed for the measured metals. Time (t) is

212   reported in hours (hrs) and concentrations in parts per billion (ppb, µg/kg) and parts per

213   million (ppm, mg/kg). Element ratios are reported by weight. Errors are reported at the 2σ

214   level.

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216   **4.   Results**

217   The ITO powder consists of irregularly shaped particles of 10-50 µm that commonly

218   are hollow and have large surface to mass ratios (Figure 1). X-ray diffraction confirmed the

219   powder to be composed of Sn-doped In_2O_3 with distinct signals also for discrete SnO_2. No

220   signals were observed for In_2SnO_5 or $In_4Sn_3O_{12}$ (Kim et al., 2006; Heward and Swenson,

221   2007). Spot analysis by EPMA confirmed the SnO_2 content of the tin-doped indium oxide to

222   vary between 2.6 and 8.0 wt% (average 3.0 wt%, n=26) and also confirmed the presence of

223   discrete SnO_2 particles that are generally less than 5µm across. The only impurity detected

224   was silicon dioxide (SiO_2) which occurs throughout at 0.4 wt% and locally reaches 2 wt%.

225   The compositions are consisted with material that has been sintered at temperatures in excess

226   of 1000 °C (Heward and Swenson, 2007), and is as such similar to industrial ITO powder

227   used for the production of sputtering targets. The wall thicknesses of the individual ITO

228   particles are up to to 3µm, which is generally thicker than the average 125 nm for ITO

229   coatings (Böni and Widmer, 2011). So while the powder is compositionally and structurally

230   similar to industrial ITO, the greater wall thicknesses lead to lower expected surface to

231   volume ratios than for particles liberated from ITO coatings. The powder furthermore

232   displays no signs of having been subjected to the densification that is involved in the

233   production of ITO sputtering targets. The particle sizes and shapes therefore differ to those

234   that can be expected to be released from ITO sputtering targets or ITO coatings during

235   production or recycling. We consider that the structural and compositional similarities are

236   reasonable matches to industrial ITO. The particle size differences and lack of densification,

237   however, are likely to lead to minor differences in the dissolution kinetics. Although the

238   dissolution speed may differ, we have no reason to believe that the metal concentrations in

239   the fluids would be substantially different.

240   The results of the dissolution experiments are presented in Figures 2-7 and the

241   supplementary data file. As per design, all samples had significant excess of undissolved ITO

242   at the termination of the experiments. Since partial dissolution is a fractional process, it is

243   appropriate at least as a first approximation, to consider the dissolution curves as power

244   functions (cf., Lánský and Weiss, 2003). Our results show very limited solubility of ITO in

245   deionized water and under simulated upper respiratory tract conditions (Gamble's solution)

246   but significant solubility in the simulated deep lung (ALF) and digestive (PBET)

247   environments. In deionized water (Figure 2), In concentrations stabilized at 134 ± 47 ppb in

248   less than 18 hours while Sn concentrations systematically remained below 0.2 ppb. Both

249   display decreasing concentrations with time, along the equations In (ppb) = 253 $t^{-0.15}$ and Sn

250   (ppb) = 8.59 $t^{-1.80}$, which can be explained by adsorption to the plastic containers (Robertson,

251   1968; Smith, 1973). The In blank was measured at 0.18 ± 0.16 ppb while the Sn blank

252   remained below 0.01 ppb.

253   Under simulated upper respiratory tract conditions (Figure 3), concentrations of In

254   and Sn remained very low. Surprisingly, Sn appeared to be taken into solution more readily

255   than In. Indium remained below 10 ppb and showed a negative correlation with time at In

256   (ppb) = 6.58 $t^{-0.22}$ ($R^2 = 0.63$), while Sn reached 60 ppb and displaying a positive correlation

257   along Sn (ppb) = 9.69 $t^{0.32}$ ($R^2 = 0.87$). The In/Sn evolved along a trend of In/Sn (w/w) = 0.68

258     $t^{-0.54}$ ($R^2 = 0.82$). As above, the negative correlation of In with time can be explained by

259   adsorption to the container walls (Robertson, 1968; Smith, 1973). The In blank was $3.39 \pm$

260   4.06 ppb and the Sn blank was 0.95 ± 0.51 ppb.

261   The deep lung environment (simulated with the ALF solution), in contrast, displayed

262   significant dissolution of the ITO (Figure 4) with maximum concentrations after 480 hrs

263   reaching 236 ppm In and 8.4 ppm Sn. The increase in concentrations of In and Sn follow best

264   fit regressions of In (ppb) = 4276 $t^{0.61}$ ($R^2 = 0.97$) and Sn (ppb) = 642 $t^{0.42}$ ($R^2 = 0.99$). The

265   In/Sn of the fluid increased over time along a best of In/Sn (w/w) = 6.66 $t^{0.18}$ ($R^2 = 0.71$),

266   showing differential dissolution of In relative to Sn.

267   The stomach environment (simulated with the PBET solution) similarly displayed

268   significant dissolution of ITO with concentrations increasing systematically over time (Figure

269   5). Maximum concentrations after 4 hours were 3.6 ppm In and 127 ppb Sn. Regressions are

270   for In (ppb) = 2092 $t^{0.34}$ ($R^2 = 0.95$) and Sn (ppb) = 72.6 $t^{0.39}$ ($R^2 = 0.93$). The In/Sn ratio

271   showed little variation over time at In/Sn (w/w) = 28.84 $t^{-0.05}$ ($R^2 = 0.36$). Blanks were

272   systematically below 1 ppb In and 0.2 ppb Sn.

273   Experiments with trypsin (Figure 6) showed In reaching a stable concentration of 901

274   ± 107 ppb in solution in less than 18 hours. The best fit correlation for In (ppb) = 876 $t^{0.01}$ is

275   not convincing ($R^2 = 0.01$). The Sn concentration displayed a decrease in concentration along

276   a trend of Sn (ppb) = 46.57 $t^{-0.33}$ (R^2 = 0.27). A slight increase in In/Sn (ppb) = 12.5 $t^{0.36}$ (R^2 =

277   0.04) over time is unconvincing. The average of 9 blank measurements yielded 1.67 ± 1.07

278   ppb In and <0.05 ppb Sn.

279   When the different results are compared (Figure 7), it is clear that by far the most

280   extensive potential for release of In and Sn from ITO is in the simulated deep lung

281   environment (Figure 7a, b). Although the dissolution rates were nearly as high in the stomach

282   environment, the much shorter particle residence time effectively limited the concentrations

283   that could be reached. Although In may be subject to further dissolution in the pancreatic

284   juice, the total fluid concentrations that can be reached during digestion remains much lower

285   than the deep lung environment. The simulated upper lung environment displays almost no

286   dissolution of In, while Sn is very weakly soluble – although at a rate that is nearly 100 times

287   lower than in the deep lung environment. Selective leaching, expressed by In/Sn is

288   particularly strong in the upper lung environment (selective leaching of Sn) and in deionised

289   water (selective leaching of In). The simulated deep lung and stomach environments as well

290   as the pancreatic juice are much less selective of metals during leaching.

291

292   **5.**   **Discussion**

293   Although In is more common in the continental crust than silver (Rudnick and Gao,

294   2003), little is known about the environmental dispersal of the most commonly used In

295   compounds (White and Hemond, 2012). Most toxicological studies focus on ITO factories,

296   where workers are exposed to particularly high concentrations of the metal in various forms.

297   While In is primarily recovered through chemical leaching, the recycling business, in

298   particular, employs mechanical abrasion (sand blasting, sanding, wet grinding) to liberate

299   ITO (Hines et al., 2013, Zeng et al., 2015; Zhang et al., 2015), releasing nano- and micro-

300   particles into the air that may be inhaled. Most medical studies consequently focus on

301 respiratory disorders, as recently evaluated by Cummings et al. (2012), who associated ITO

302 with pulmonary alveolar proteinosis, pulmonary fibrosis, emphysema, and pneumothoraces.

303 Although Zheng et al. (1994) suggested that In is poorly absorbed in the body, Nagano et al.

304 (2011) suggested (based on a study of rats) that in addition to the lungs, the metal may also

305 concentrate in the spleen, kidney and liver. The study by Chen (2007) suggests that some In

306 is eventually excreted, and while the study by Morrow et al. (1957) suggests a short

307 biological half-life (in the order of a couple of weeks), Amata et al. (2015) consider that

308 actual residence times in humans to be as high as 8 years. It is worth noting that while the

309 study by Morrow et al. (1957) was based on a single dose of In, Amata et al. (2015)

310 considered the effects of long term exposure, a situation that is much more relevant to

311 workers exposed to ITO.

312   Sintering of ITO is a solid-state process that aims to generate a technological material

313 by solid-state diffusion and particle annealing. It is an inherently inhomogeneous process that

314 leads to a metastable product (Heward and Swenson, 2007). The observed structure and

315 compositional variability of the ITO powder is consistent with the expected variability in

316 industrial products and the structure of ITO coatings (Thirumoorthi and Thomas Joseph

317 Prakash, 2016). The presence of discrete SnO_2 particles is consistent with incomplete reaction

318 or local supersaturation, as explained by Kim et al. (2006). The particles are coarser than

319 those that are likely to be liberated from ITO coatings, and as the dissolution rate is likely to

320 be a function of the surface area, this implies that the dissolution is likely to be faster than

321 during our experiments. The structure and compositional variation, however, are sufficiently

322 similar to suggest that our results provide a reasonable analogue of ITO particles that are

323 liberated from the production and recycling of flat screen devices.

324   Sintered ITO remains a hardly soluble compound when compared to other In

325 compounds such as In-phosphide, In-arsenide In-trichloride and In-acetate (Chapin et al.,

326   1995; Oda, 1997; Tanaka, 2004, Lee et al., 2016). Our study demonstrates that ITO is nearly

327   insoluble under simulated upper respiratory tract conditions and in deionized water, while it

328   displays some dissolution in the simulated deep lung and stomach environments.

329   Surprisingly, the In concentrations in the simulated upper respiratory tract conditions

330   (Gamble's solution), deionized water, and deionized water with trypsin display negative

331   correlations with time, suggesting that the metal is removed from solution over time.

332   Robertson (1968) and Smith (1973) documented that In is readily lost from solution unless

333   kept at low pH. They concluded that the metal adsorbs to (or is absorbed into) plastic

334   containers. All of these solutions have near neutral pH, and we consider metal loss to the

335   containers to adequately explain the negative trends.

336   When inhaled as airborne micro- and nano-particles (Figure 8), our tests with

337   Gamble's solution suggest that ITO is likely to largely remain as solid particles as long as

338   they rest in the upper respiratory tract or tracheobronchial tree. The ITO particles could

339   possibly cause some mechanical irritation but they remain fairly inert in this environment.

340   Very minor differential leaching of Sn is possible, although this is unlikely to be of medical

341   concern. It is interesting that the solubility of In is much lower than in deionised water,

342   indicating that the solubility is negatively affected by the dissolved salts.

343   Upon contact with the more acidic fluids associated with the deep parts of the lungs

344   (the bronchioles and alveoli), the ITO will release In^{3+} and Sn^{4+} into solution. Our

345   experiments did not plateau at a saturation level, which at least must be higher than the 236

346   ppm In and 8.5 ppm Sn maxima measured at 480 hours. Our results suggests that In in this

347   environment is able to transfer into the bloodstream for wider dissemination through the

348   human body. The low, but systematic solubility combined with the very long potential

349   residence times for ITO in the deep parts of the lungs suggest that this is the dominant route

350   of transfer of metals into the bloodstream. As outlined above, the United States recommended

351 inhalation exposure limit indicates that typically 0.67-0.83 mg In could be inhaled an eight

352 hour working day, leading to a total inhalation of 13.4 – 16.6 mg over a period of 20 working

353 days. If 25-45% is considered to accumulate in the deep lungs (Jaques and Kim, 2000), the

354 accumulation over this period would amount to 3.4 – 7.5 mg ITO, of which 2.5 – 5.6 mg

355 would be In. Our experiments reached fluid concentrations of 236 ppm In, which equates to

356 the dissolution of 2.36 mg In in the 10 ml test solution over a period of 20 days. If the amount

357 of extravascular lung water in healthy adults is considered to be 255 ml, as estimated by

358 Wallin and Leksell (1994), the total volume of fluids would be able to dissolve around 60 mg

359 In over this period. While the actual In concentrations that may be reached in the deep lung

360 fluids would depend on the ITO accumulation rates, fluid availability and clearance rates, the

361 scale and scope of our experiments appear entirely realistic for human intake.

362   The ITO is also likely to slowly decompose in the acid environment of the stomach

363 (Figure 8) leading to the release of In and, to a lesser extent Sn. As for the deep lung

364 environment, the concentrations didn't plateau, and the solubility must at least exceed the

365 measured maximum concentrations of 3 ppm In and 120 ppb Sn. However, it is notable from

366 other laboratory experiments that the solubility of In appears to be strongly pH dependent

367 (Smith, 1973), and it is likely that the dissolution rate will vary substantially during the

368 digestive cycle. Minor further decomposition may occur in the pancreatic juice, where trypsin

369 (and possibly other enzymes) facilitate dissolution. The digestive tract, consequently, offers

370 another route for intake of the In and Sn. However, despite comparable rates of dissolution to

371 the deep lung environment, the much shorter residence times lead to much lower

372 concentrations. The metal transfer through the digestive tract would consequently be much

373 less significant.

374   While we are not in a position to properly evaluate the wider toxicological effects of

375 ITO, we note that the effects of inhalation is likely not to be restricted to the lung

376 environment. Over time, In and Sn become mobilized into the bloodstream through the

377 bronchioles and alveoli, and therefore circulate more widely throughout the body. Once taken

378 into the bloodstream, given the low pH of the deep lung fluids and the stomach acid, the In

379 would be likely to take the form of ionic In^{3+} and bind to plasma transferrin (Hosain et al.,

380 1969) before eventually being deposited in the kidneys (Smith et al., 1978). The actual

381 concentrations that can be reached will primarily depend on how fast the deep lung fluids are

382 replenished and cleared. Ionic In in the bloodstream can be expected to have similar health

383 effects as other soluble In-salts, particularly Lewis acids such as In-trichloride. Although In

384 may eventually be excreted (Chen, 2007), it is important to develop an understanding of the

385 potential health effects that could occur more widespread throughout the body through

386 prolonged exposure to ITO.

387   With the wider environmental dispersion as ITO hits the domestic waste routes, it is

388 likely that adverse health effects may spread much more widely than to ITO factory workers.

389 The most likely people at risk would be scrapyard workers and people involved with

390 recycling of electronic and domestic waste (Zeng et al., 2015), particularly in developing

391 countries where environmental controls are poorly developed (Robinson, 2009; Lim and

392 Schoenung, 2010). While the effects of Sn are well constrained, the largely unknown

393 behavior of In in the surface environment is worrying. It is surprising that In is considered to

394 be fairly harmless, when most of the nearest neighbors in the periodic table (Sn, Cd, Hg, Tl,

395 Pb) are associated with severe adverse health and environmental effects. The wide global

396 dissemination of In leads to concerns about the potential risks that could be caused by the

397 disposal of electronic devices with flat screen displays through the domestic waste routes.

398 Further work is urgently needed to understand how the likely widespread release of In from

399 ITO may affect the environment.

400

17

6. Conclusions

While ITO appears to be nearly inert in the upper parts of the respiratory system, In and Sn are likely to be released into fluids in the deep parts of the lungs. At current exposure limits, accumulation rates could potentially reach 50 mg in less than a year for workers exposed to ITO during daily 8 hour working shifts. Concentrations in deep lung fluids could potentially exceed 236 ppm In and 8.5 ppm Sn leading to significant transfer of the metals into the bloodstream. In the digestive tract, In and Sn are also released from ITO in the stomach, where further release may be facilitated by enzymes in the pancreatic juice. However the much shorter residence time indicates a much lower risk of metal uptake through digestion.

Dissolution of ITO from inhaled nano- and microparticles in the deep lung fluids is likely to be the most significant mechanism for transfer of In (and Sn) into the bloodstream. As dissolved metal ions circulate through the human body, the exposure may lead to health damage outside of the environment of the lungs. In this context, the poor knowledge of the environmental properties and potential toxicity of In are immediate causes of concern with respect to the distribution of In-compounds across the human society.

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Figure captions

596 **Figure 1.** Backscattered electron image (COMP, compositional contrast) of a polished block

597 of the ITO powder. The image shows ITO particles (bright) embedded in epoxy resin (dark)

598 and polished to a flat surface. Particle outlines represent transects through individual

599 particles. Particles are generally rounded aggregates of hollow spheres with high surface to

600 volume ratios. The scale bar is 10 μm.

601

602 **Figure 2**. Concentrations of In (A) and Sn (B) and the In-Sn ratio (C) measured in deionized

603 water in contact with ITO powder. The negative correlations of In and Sn with time are likely

604 to be caused by sorption of metals to the container walls (Robertson, 1968; Smith, 1973).

605

606 **Figure 3**. Concentrations of In (A) and Sn (B) and the In-Sn ratio (C) measured in simulated

607 upper respiratory tract fluids (Gamble's solution) in contact with ITO powder. As for figure

608 2, the negative correlation of In with time is likely to be caused by sorption to the container

609 walls. The substantial decrease in In/Sn over time is a combined effect of In removal and Sn

610 dissolution.

611

612 **Figure 4**. Concentrations of In (A) and Sn (B) and the In-Sn ratio (C) measured in simulated

613 deep lung fluids (the ALF solution) in contact with ITO powder. In and Sn display strong

614 positive correlations with time. The evolution in In/Sn demonstrates selective dissolution of

615 In.

616

617 **Figure 5**. Concentrations of In (A) and Sn (B) and the In-Sn ratio (C) measured in the

618 simulated stomach acid (the PBET solution) in contact with ITO powder. In and Sn display

619   strong positive correlations with time. This environment is not particularly selective in the

620   dissolution of In and Sn.

621

622   **Figure 6**. Concentrations of In (A) and Sn (B) and the In-Sn ratio (C) measured for deionized

623   water with trypsin in contact with ITO. The results indicate that trypsin may facilitate the

624   dissolution of In in the pancreatic fluid to concentrations that are nearly as high as those in

625   the simulated stomach acid.

626

627   **Figure 7**. Comparison of the dissolution of In (A), Sn (B) and the In-Sn ratio (C) for the

628   different experiments illustrated in figures 2-6. The figure highlights the significance of the

629   deep lung environment in the dissolution of inhaled ITO. Concentrations obtained by

630   dissolution in stomach acid and the pancreatic juice (trypsin assisted), while potentially also

631   significant, are limited by the shorter particle residence time.

632

633   **Figure 8**. Schematic illustration of the main routes of ITO uptake in the human body. The

634   most significant route of uptake is through inhalation where the most significant metal

635   transfer is likely to occur in the deep lung fluids. Digestion is another potential route for

636   metal uptake, although the shorter residence time is likely to limit the magnitude of metal

637   transfer.

638

Table 1
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Chemical compound	Chemical formula	ALF solution	Gamble's solution	PBET solution
Magnesium chloride	$MgCl_2$	0.05 g/L	0.10 g/L	-
Sodium chloride	NaCl	3.20 g/L	6.00 g/L	-
Potassium chloride	KCl	-	0.30 g/L	-
Disodium hydrogen phosphate	Na_2HPO_4	0.07 g/L	0.13 g/L	-
Sodium sulphate	Na_2SO_4	0.04 g/L	0.07 g/L	-
Calcium chloride dihydrate	$CaCl_2$ x $2H_2O$	0.13 g/L	0.37 g/L	-
Sodium acetate	$NaC_2H_3O_2$	-	0.57 g/L	-
Sodium hydrogen carbonate	$NaHCO_3$	-	2.60 g/L	-
Sodium citrate dihydrate	$Na_3C_6H_5O_7$ x $2H_2O$	0.08 g/L	0.10 g/L	0.50 g/L
Sodium hydroxide	NaOH	6.00 g/L	-	-
Citric acid	$C_6H_8O_7$	20.80 g/L	-	-
Glycine	NH_2-CH_2-COOH	0.06 g/L	-	-
Sodium tartrate dihydrate	$Na_2C_4H_4O_6$ x $2H_2O$	0.10 g/L	-	-
Sodium lactate	$NaC_3H_5O_3$	0.10 g/L	-	-
Sodium pyruvate	$NaC_3H_3O_3$	0.10 g/L	-	-
Pepsin		-	-	1.25 g/L
Malic acid	$C_4H_6O_5$	-	-	0.50 g/L
Lactic acid	$C_3H_6O_3$	-	-	420 µL/L
Acetic acid	CH_3COOH	-	-	500 µL/L
pH (adjusted with concentrated HCl)		4.5	7.5	4.0

Table 1. Weight and volumes of material for the simulation of the deep lung environment (artificial lysosomal fluid, ALF), the upper respiratory tract (Gamble's solution) and the stomach environment (physiologically based extraction test, PBET). The ALF and Gamble's solutions follow the formulations of Colombo et al. (2008) while the PBET follows Ruby et al. (1996).

Andersen et al.   Figure 1   ½ page width

$In = 253\, t^{-0.15}$
$R^2 = 0.59$

$Sn = 36.6\, t^{-2.32}$
$R^2 = 0.26$

$In/Sn = 361\, t^{0.66}$
$R^2 = 0.36$

Plot A (In, ppb vs Time, hours):
$$In = 6.58\, t^{-0.22}$$
$$R^2 = 0.63$$

Plot B (Sn, ppb vs Time, hours):
$$Sn = 9.69\, t^{0.32}$$
$$R^2 = 0.87$$

Plot C (In/Sn, weight vs Time, hours):
$$In/Sn = 0.68\, t^{-0.54}$$
$$R^2 = 0.82$$

A

$In = 4{,}276\ t^{\,0.61}$
$R^2 = 0.97$

B

$Sn = 642\ t^{\,0.42}$
$R^2 = 0.99$

C

$In/Sn = 6.66\ t^{\,0.18}$
$R^2 = 0.71$

A

$In = 2,093\ t^{0.34}$

$R^2 = 0.95$

B

$Sn = 72.6\ t^{0.39}$

$R^2 = 0.93$

C

$In/Sn = 28.8\ t^{-0.05}$

$R^2 = 0.36$

A

$In = 876\ t^{0.01}$
$R^2 = 0.01$

B

$Sn = 46.6\ t^{-0.33}$
$R^2 = 0.27$

C

$In/Sn = 12.5\ t^{0.36}$
$R^2 = 0.04$

Time, hours

LCD production / recycling Release of In-Sn oxide (ITO)

Inhalation
Digestion

Interactions with the human body

Irritation caused by inhaled ITO particles

Release of In^{3+} and Sn^{4+} in deep lung

Release of In^{3+} and Sn^{4+} in stomach

Further release of In^{3+} after addition of pancreatic juice