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# **Exposure Potential and Health Impacts of Indium and Gallium, Metals Critical to Emerging Electronics and Energy Technologies** Sarah Jane O. White, James P. Shine

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#### **Abstract**

The rapid growth of new electronics and energy technologies requires the use of rare elements of the periodic table. For many of these elements, little is known about their environmental behavior or human health impacts. This is true for indium and gallium, two important metals in electronics and new energy technologies. Increased environmental concentrations of both indium and gallium create the potential for increased environmental exposure, though little is known about the extent of this exposure. Evidence is mounting that indium and gallium can have substantial toxicity, including in occupational settings where indium lung disease has been recognized as a potentially fatal disease caused by the inhalation of indium particles. This paper aims to review the basic chemistry, changing environmental concentrations, potential for human exposure, and known health effects of indium and gallium.

# **Introduction**

New electronics and energy technologies create demand for an ever-increasing use of the rarer elements in the periodic table. This article reviews two such elements, indium and gallium, which have seen significant increase in use in recent decades. Indium has come into use in the past 30-40 years as an integral material in flat panel displays, LEDs, and photovoltaic cells, and world production has increased by almost 30 times between 1984 and 2014*(1)*. Similarly, gallium is used in integrated circuits, LEDs, and solar cells, for example, and use has increased by 13 times in that same time span*(2)*.

Perhaps because their use is increasing so rapidly, there is a clear lag in the understanding of the environmental behavior and human health impacts of these metals. However, evidence is mounting that there are serious health impacts of many of them, particularly from occupational exposures. Increased use may result in increased human exposure in the workplace. Environmental exposures may also increase as environmental concentrations are altered by metal releases during processing, upstream mining and smelting processes, consumer use, or end-of-life recycling or disposal. Particularly during electronic waste recycling, vulnerable populations such as children are exposed, creating a serious environmental health disparity *(3)*.

This paper aims to review the changing environmental concentrations, potential for exposure, basic chemistry, and known health effects of indium and gallium, two important metals in electronics and new energy technologies. We aim to provide a snapshot of the situation for each metal, which may allow clinicians and environmental health and safety (EHS) representatives to appropriately advise those who are likely to be exposed to these metals, and to recognize symptoms of high exposure as we continue to learn about the health impacts. We also stress the importance of monitoring for exposure to these elements when working with them, despite a lack of regulatory guidance. For example, while neither indium nor gallium is presently regulated in the United States, indium lung disease is recognized as a potentially fatal condition in workers exposed to indium particles. In the case of these metals, a lack of regulation does not denote safety; instead, a lack of regulation results from a lack of information.

# **Indium**

### *Chemistry*

Indium is a group III element, below aluminum (Al) and gallium (Ga), and above thallium (Tl) in the periodic table. It exists primarily in the  $+3$  oxidation state, and has some potential redox ability to the  $+1$  state in extreme conditions. Its ionic radius is 0.80Å*(4)*. The speciation and complexation of a metal influences its mobility, behavior, and toxicity in the environment and in the human body. In aqueous conditions in the environment, indium tends to complex with hydroxide, with free  $In<sup>3+</sup>$  predominating at pH values below 4.5, and  $In(OH)<sub>3</sub>$ <sup>0</sup> predominating at the neutral pH values of natural water bodies*(4)*. In the human body, complexation with hydroxide may also be expected, again existing as free In<sup>3+</sup> in low pH environments like the stomach, and In(OH)<sub>3</sub><sup>0</sup> in more neutral environments like blood. However, in low pH environments, if Cl is significantly high, In(III)-chloride or hydroxychloro complexes may exist *(4)*. And although this relatively hard ion tends to complex with hard ligands such as OH, F, and acetate, indium may also complex with softer ligands such as HS- *(4)*, which may be plentiful in certain reservoirs of the body. Organic ligands may also play an important role in indium speciation in both the natural environment and the human body *(5, 6)*.

There is a lack of information available about complexes with bicarbonate or carbonate *(4)*, another ligand of potential importance in the natural environment and the human body. While complexation is generally understood, there is still a significant degree of uncertainty since complexation constants are based on relatively few studies.

Indium is relatively insoluble; Wood & Samson *(4)* report that waters in contact with the rare mineral dzhalindite  $[In(OH)<sub>3</sub>(s)]$  would have at most 5  $\mu$ g/L (~50 nmol/L) indium, and environmental concentrations are significantly lower than this, on the order of picomolar for freshwaters and oceans. Under anoxic conditions,  $In<sub>2</sub>S<sub>3</sub>$  may limit indium mobility due to its lower solubility. In low pH reservoirs in the body, solubility would be expected to be higher than in neutral pH systems. Indium is volatile, appearing to be slightly less volatile than lead (*(6)* and references therein), which has implications for its long-term transport and exposure routes.

# *Uses*

Indium is used mainly in indium tin oxide (ITO) coatings for flat panel and liquid crystal displays *(7)*. It is also used in LEDs and high-efficiency photovoltaic cells, markets that have seen rapid growth and are predicted to continue expanding *(6, 8)*. A relatively small use of indium, though one that could lead to significant exposure, is the use of a radioisotope <sup>111</sup>In for medical imaging and biodistribution studies *(7, 9)*.

# *Changing environmental concentrations*

Indium occurs at an average concentration of 52 μg/kg in the earth's crust *(10, 11)*. This is approximately the same concentration as mercury and silver, 2 orders of magnitude less than arsenic, and 3 orders of magnitude less than lead. Natural waters contain picomolar (~0.1 ng/kg) concentrations of indium *(6)*, and the atmosphere at the South Pole has been measured to contain 53  $\text{fg/m}^3$  (12). Sulfide minerals and tin oxide tend to have enriched levels of indium, typically in the range of 10 mg/kg; indium is economically recovered from zinc and lead ores and does not typically exist as its own mineral *(4, 6, 13)*. Coal has average indium concentrations of 100 μg/kg *(13)*.

There is evidence that human activity has led to changes in indium concentrations in the environment at both regional and local scales. For example, evidence from a peat core in the Northeastern United States suggests that indium deposition from the atmosphere rose by a factor of 12.5 times between the late 1800s to the 1960s, before falling back to similar levels as the late 1800s in the present day*(14)*. This regional change in atmospheric concentrations is thought to be due to indium releases from coal combustion and the smelting of lead, zinc, copper, and tin sulfides throughout the early part of the  $20<sup>th</sup>$  century, followed by a decline in emissions from these sources following particulate emissions regulations in the 1970s *(14)*. On a more local scale, researchers have measured groundwater concentrations of indium at a Semiconductor Industrial Park to be elevated by 1,000-fold as compared to a neighboring site in Taiwan *(15)*. Additionally, a stream influenced by acid mine drainage from a lead mining area in Colorado contains indium levels 10,000 times higher than natural concentrations *(16)*.

## *Potential for exposure*

The increased use and subsequent changes in environmental concentrations of indium suggest the possibility for increased human exposure. Perhaps the most pressing

exposure is occupational. In particular, when workers grind and polish indium or indium tin oxide (ITO) targets that are used in semiconductor manufacturing, they are exposed to fine indium particles at concentrations 1-100 million times what a person may normally be exposed to in the atmosphere *(17, 18)*. Additionally, in the course of semiconductor manufacturing, high exposure – up to 1 trillion times natural exposures – can occur while resurfacing ITO sputter targets between deposition runs, and while cleaning the walls and chamber parts of sputter chambers, either chemically or by abrasive blasting *(8)*. As nanoscale applications of indium grow *(19, 20)*, exposure to nanoparticles may be of increasing concern due to the potential for increased bioavailability and unique toxic properties as compared to macromaterials of the same makeup. Other potential occupational exposures may occur during the manufacture of inorganic indium compounds *(8)*, the recycling of e-waste, and upstream mining and smelting that produce indium metal or simply contain indium as a byproduct of the primary metal recovered. Another route of exposure to indium is the intentional introduction of radioisotope  $\frac{111}{n}$ in medicine as an imaging agent or for biodistribution studies.

Environmental exposure is also possible. Areas of high local concentrations could occur near mines and smelters, recycling facilities, coal-fired power plants, and semiconductor manufacturing *(6, 8, 14-16, 21, 22)*, posing a threat of increased exposure to local residents. Additionally, the study of atmospheric deposition to a bog in Massachusetts suggests that atmospheric concentrations have varied by as much as 30x over the past 50 years *(14)*. The study suggests that present concentrations have decreased to pre-1900 values, but that peak exposure may have occurred during 1960s and 1970s *(14)*. There is presently no data about exposure to indium from the direct use of consumer electronics that we are aware of.

In the US, there is a recommended exposure limit of 0.1 mg indium/m<sup>3</sup> (8, 23, *24)*. However, there is no *regulated* limit (in the form of a permissible exposure limit) set by the US Occupational Safety and Health Administration *(8)*. In Japan, the respirable exposure limit is set at  $0.0003$  mg/m<sup>3</sup> (25). This difference of three orders of magnitude between the US and Japanese limits is remarkable, and likely reflects both an incomplete understanding of worker exposure and subsequent health impacts, and regulations struggling to keep pace with knowledge of the health impacts of indium. This discrepancy is another reminder to use precaution with elements like indium – even absent government regulation – since toxicity and behavior are still poorly understood.

## *Known human effects*

Indium lung disease is recognized as a potentially fatal disease caused by the inhalation of indium-containing particles *(17, 26, 27)*. It is characterized by pulmonary alveolar proteinosis (PAP) that can turn into fibrosis and may include emphysema *(27)*. Even in the absence of a full presentation of lung disease, epidemiological studies have shown that indium workers have increased incidence of lung lesions, reduced diffusing capacity, and interstitial lung disease biomarkers such as Krebs von den Lungen (KL)-6 and surfactant protein (SP)-D *(17, 28-31)*. Increased exposure has been linked with increased indium concentrations in blood serum or plasma, which has been linked with poor health outcomes *(17)*. In acute cases of indium lung disease, systemic effects such as emaciation, liver damage, and enlarged spleen have also been seen *(32)*.

InP is a probable human carcinogen *(33, 34)*. In animals, pulmonary toxicity has been seen for a wide array of indium-containing compounds, along with testicular damage and developmental toxicity of  $InCl<sub>3</sub>$ , InAs, and InP ( $(6, 8)$ ) and references therein). Comparative studies with  $As_2O_3$ ,  $NaAsO_3$ ,  $As_2Se_3$ , InP, InCl<sub>3</sub>, GaAs, AlGaAs, or CuGaSe<sub>2</sub> suggest that indium itself is responsible for significant toxicity  $(35-37)$ . Few studies have been done to elucidate the effects of low-level and chronic exposure to indium compounds.

There is evidence that a mechanism of indium toxicity is inhibition of heme synthesis, through direct or indirect inhibition of the delta-aminolevulinic acid dehydratase (ALAD) enzyme *(38-42)*.

# *Biomarkers and monitoring*

Blood serum or plasma is typically used for monitoring occupational exposure, and a correlation has been found between blood serum or plasma and health outcomes such as lung lesions and increased inflammatory markers in indium workers *(17, 27-29, 31, 43)*. Among indium workers *(17)*, blood plasma levels ranged from close to 0.01 to 100 μg/L. In a man who died due to indium inhalation *(32)*, the blood serum level was 290 μg/L. In Japan there is a threshold of  $3 \mu g/L$  for blood serum at which point work restrictions are considered *(25)*.

In indium workers, blood plasma indium concentrations correlate better with chronic exposure than current exposure *(17)*, a reflection of inhaled indium's relatively long lifetime in the body. This is also reflected by the fact that workers formerly exposed to indium (median time since exposure  $= 4.6$  years) have similar serum levels as current workers *(28, 31)*. Further, hamsters exposed intratracheally to ITO or indium oxide showed increasing serum indium up to 78 weeks after the final exposure *(44)*. This is in contrast to several animal studies that suggest a much shorter half-life for orally, intravenously, or intratracheally administered indium compounds of days to weeks (*(42, 45-47)* and references therein). Exposure route and chemical form may play a role in these diverse half-life estimates; further study is warranted. It is clear that blood serum levels are not necessarily reflective of present working conditions; in order to understand current exposures and adjust safeguards accordingly, it is important to monitor current air concentrations.

Distribution throughout the body depends on the chemical form of indium; ionic indium accumulates in kidney, while colloidal indium accumulates in the liver, spleen, and reticuloendothelial system (*(47)* and references therein). Indium is transported in blood, bound to transferrin *(46)*, largely in plasma *(47)*. It is found in the lung tissue of indium workers exhibiting lung disease *(26)*, and systemic effects suggest distribution to other organs *(32)*. Table 1 provides a summary of half-life, distribution, and transport in the body.

# *Discussion & Summary*

Increasing exposure to indium is a concern, especially in occupational settings, but also in close proximity to industries such as mining and smelting, coal combustion, and semiconductor manufacture. Serious human health effects have been shown for acute exposure, particularly through inhalation of indium particles. Indium's apparent

long lifetime in the body after inhalation is a significant concern, as is the carcinogenic potential of indium compounds. There is a lack of information, however, for indium's basic environmental behavior, and for environmental exposure to this metal, including the main routes and sources of exposure for general populations. Studies are lacking regarding exposure to indium via ingestion or through the skin, and the effects of low level and chronic exposures are not well characterized. Additionally, knowledge of health impacts needs to be better translated into recommended and regulatory exposure limits, given the discrepancy between the recommended limits in the US versus Japan. Because toxicity is still not well understood, care should be taken to monitor and minimize exposure through the use of good laboratory and occupational practices and use of personal protective equipment, not only in the known situations of exposure cited above, but in any situation dealing with indium.

# **Gallium**

# *Chemistry*

Gallium is a group III element, situated below Al, and above In and Tl in the periodic table. It exists as a liquid near room temperature  $(29^{\circ}C)$  and has a boiling point of 2,204<sup>o</sup>C) (48). It has a +3 oxidation state, and an ionic radius (0.62Å) similar to  $Al^{3+}$ and  $\text{Fe}^{3+}$ , causing it to substitute for these ions in common minerals (4), and potentially in proteins in the human body. Gallium is thought to behave similarly to aluminum in natural waters, though it is more particle reactive *(49-52)*. Similar to indium, gallium tends to complex with hard ligands like OH,  $F$ , and acetate. Free Ga<sup>3+</sup> predominates at pH values less than 3, while  $Ga(OH)^4$  predominates at pH values greater than 4.5 (4). This suggests that in neutral environmental waters, and in all reservoirs of the human body except the stomach,  $Ga(OH)^4$  would predominate. Gallium is less likely to complex with Cl<sup>-</sup> or HS<sup>-</sup> than indium  $(4)$ , but organic molecules may influence its speciation in natural waters and human reservoirs *(53)*. (Gallium's tendency to form polymeric complexes makes the determination of stability constants for monomeric complexes such as  $GaOH<sup>2+</sup>$  or  $Ga(OH)<sub>3</sub><sup>0</sup>$  difficult, and thus reported constants have a high degree of uncertainty *(4)*.) For more complete details of aqueous behavior, see Wood & Samson *(4)*.

Gallium is fairly insoluble. Available solubility constants for GaOOH(s) suggest that water in contact with this solid would have a maximum of 30 ng/L ( $\sim$ 500 pmol/L) *(4)*. This is slightly higher than typical environmental aqueous concentrations from ~0.2 - 10 ng/L (~3 – 100 pmol/L) *(51, 54)*. Gallium is slightly less volatile than indium *(6, 55, 56)*.

#### *Uses*

Gallium is used primarily as GaAs or GaN in integrated circuits and optoelectronic devices such as laser diodes, LEDs, photodetectors, and solar cells. Gallium is also used in copper indium gallium diselenide (CIGS), a thin-film photovoltaic material *(48, 57)*. Gallium is additionally used in medicine, where the radioisotopes  $Ga^{67}$  and  $Ga^{68}$  are used as imaging agents, and stable gallium compounds are used as chemotherapeutic agents *(58, 59)*. Stable gallium compounds are also used in the treatment of hypercalcemia, a life-threatening metabolic disorder in cancer patients *(58)*, and as antimicrobial agents *(60)*.

# *Changing environmental concentrations*

Gallium exists at an average crustal concentration of 17 mg/kg, similar in concentration to lead, and 3 orders of magnitude higher than indium *(11, 61, 62)*. Natural freshwaters contain picomolar to 100s of picomolar concentrations of gallium, and seawater contains picomolar to 10s of picomolar concentrations of gallium *(49-52, 54,*  63-66). The atmosphere at the South Pole contains <1.1 pg/m<sup>3</sup> (12). Gallium is enriched, up to about 50 mg/kg, in bauxite and zinc sulfides *(48)*. Concentrations in coal average about 5 mg/kg (*(67)* and references therein).

Like indium, there is evidence that human activity leads to changing environmental concentrations of gallium on both regional and local scales. For example, historical deposition to remote lakes in Sweden show that acid-leachable gallium concentrations increased from  $\sim 100$  mg/kg pre-1930s to  $\sim 160$  mg/kg in the late 1970s, then decreased slightly to ~120 mg/kg by the early 2000s *(68)*. This profile was hypothesized to be due to long-range atmospheric transport from European industrialization. Gallium is also liberated at local scales through semiconductor processing and mining activities. Concentrations of gallium are 1,000-fold higher in groundwater near a semiconductor industrial park in Taiwan than in a nearby area *(15)*. In another area of Taiwan, gallium was measured to be 2.5x higher downwind than upwind from a semiconductor and optoelectronics industrial complex in ultrafine particles (0.18-1.0 μm) *(22)*. Shiller & Frilot *(49)* found gallium concentrations 500x higher in acid mine drainage from zinc mining than in a large sampling of California streams.

# *Potential for exposure*

As with indium, occupational exposure to gallium is of significant concern. For example, operators and engineers in major semiconductor companies in the Hsinchu Science-based Industrial Park in Taiwan are exposed to ~5x what office workers at the same companies are exposed to, and ~30,000x higher than what humans may be exposed to naturally *(18, 69)*. Occupational exposure to gallium is less well studied than for indium, but given similarities in how gallium and indium are processed, one may expect to find high exposure in a variety of tasks such as sandblasting GaAs or GaN ingots, grinding and polishing gallium wafers, and cleaning of work areas and chamber parts *(58, 70)*. Other potential occupational exposures may occur during the manufacture of inorganic gallium compounds, the recycling of e-waste, and upstream mining and smelting of gallium metal or of primary metals that contain gallium as a byproduct. Another route of exposure to gallium is the intentional introduction of gallium in medicine as an imaging agent or as a chemotherapeutic agent.

As with indium, areas of high local concentrations could occur near mines and smelters (49), recycling facilities, coal-fired power plants, and semiconductor manufacturing *(15, 22)*, posing a threat of increased exposure to local residents. Additionally, the study of historical sediment concentrations in lakes in Sweden suggests that exposure to Ga presently from environmental sources is higher than it was in the

1930s, with peak exposure occurring during the late 1970s *(68)*. There is presently no data about exposure to gallium from the use of consumer electronics that we are aware of.

There are presently no government regulated or recommended exposure limits for gallium, as far as we know.

# *Known effects*

While studies of gallium toxicity in humans are largely lacking, animal studies have shown significant toxicity, and use of gallium as a chemotherapeutic and antimicrobial agent suggests some inherent toxicity. There is evidence of increased lipid peroxidation in workers exhibiting elevated urine gallium levels *(71)*. While elevated levels of Ga have been observed in the urine and blood of semiconductor workers *(22, 71)*, making a link with health outcomes has not been attempted, to our knowledge.

Two case reports in the literature describe acute poisoning from exposure to gallium in the laboratory. In one case, a research chemist was exposed to fumes from gallium fluoride crystals, and developed a skin rash and neurological pain and weakness of her right arm and neck *(72)*. In the other case, an undergraduate doing research in a chemistry laboratory was exposed to fumes from gallium compounds  $(Ga_2Cl_4$  and  $GaCl<sub>2</sub>(4-Mepy)<sub>2</sub>(O<sub>2</sub>CC<sub>6</sub>H<sub>5</sub>)$ ) over the course of 1.5 years, and was splashed in the eye when washing out a flask containing these compounds. She developed a rash, increased heart rate, shortness of breath, vertigo and headaches, which progressed to leg tremors and blackouts within 6 weeks *(73)*. This was diagnosed as acute gallium poisoning, though care must be taken to account for the potential toxic effects of the other compounds potentially present; for example, 4-methylpyrridine (4-Mepy) can also cause skin irritation and shortness of breath *(74)*.

Gallium's use in medicine as a chemotherapeutic agent and for the treatment of hypercalcemia can give some insight into toxic effects. Gallium tends to localize to tumors, and cause cell death via interference with iron metabolism, as well as other mechanisms *(58)*. Gallium has relatively low toxicity when compared to its efficacy in fighting these serious diseases; however, side effects can be significant. Typical doses for cancer treatment are 300 mg/m<sup>2</sup>/day continuous infusion for 5-7 days and for hypercalcemia are 200 mg/m<sup>2</sup>/day continuous iv infusion for 5 days (58, 75, 76). These levels are generally well tolerated, but side effects include renal impairment, diarrhea, anemia, nausea and vomiting, and to a lesser extent blindness and auditory toxicities, pulmonary infiltrates, hypoxemia, fever, leukopenia, and cardiac events (*(58, 59, 75, 76)* and references therein). One clinical trial resulted in two deaths that may have been related to the gallium treatment*(59)*.

Gallium mimics ferric iron and binds to transferrin, the transport protein for iron *(58, 59)*. However, it does not have the redox potential that iron does, and interferes with protein synthesis, inhibits aminolevulinic acid dehydratase (ALAD) in the heme pathway, and alters gene expression *(58, 77)*. The exact mechanisms of localization and therapeutic action of gallium are not completely understood, nor are the potential longterm effects of medicinal exposure.

Gallium has also shown toxicity in animal studies, including pulmonary toxicity of GaAs and copper indium gallium diselenide (*(58, 59, 78)* and references therein), and immunosuppressive effects, renal and testicular toxicity of GaAs (*(58, 59)* and references therein). Gallium nitrate has shown developmental toxicity in mice *(58, 59)*. GaAs is

classified as human carcinogen *(70)*, largely because of the known carcinogenic effects of arsenic, though the antimicrobial and chemotherapeutic properties of gallium compounds suggest that gallium could play a role in carcinogenesis *(58)*. In attempts to determine whether GaAs toxicity is due solely to arsenic, comparative studies have been performed with other arsenic- and gallium-containing compounds; they indicate that gallium does not contribute significantly to the lung toxicity of GaAs. However, gallium may cause testicular toxicity, and does have a significant effect on the immune system (*(58)* and references therein). In general, inhalation or intratracheal exposure appear to be much more toxic than oral exposure for GaAs *(58)*.

A number of helpful reviews have been published on gallium's toxic effects and its use in medicine. We refer the reader to, for example, Chitambar 2010*(58)*, Fowler & Sexton 2007*(59)*, and the International Agency for Research on Cancer report on Gallium Arsenide*(70)*.

#### *Biomarkers and monitoring*

Gallium has been measured in blood and urine. Liao et al *(79)* report blood gallium averages of 0.51 μg/L in workers exposed to gallium, similar to a control group (office workers in the same factories), who had blood levels of 0.48 μg/L Ga. Gallium levels in the urine of those workers were significantly higher than in the control group  $(0.24 \mu g/L \text{ vs. } 0.15 \mu g/L)$ . Another study reported significantly higher gallium concentrations in operators and engineers at two different semiconductor companies than in administrators in the same companies (10.15 and 9.06 μg/L vs. 1.32 μg/L), which were in turn correlated with metal concentrations in inhalable air of these workers and referents *(18)*. Elevated levels in urine have been linked with increased biomarkers for lipid peroxidation *(71)*, but other health outcomes have not been linked with biomarkers. It is important to gather more information about the link between exposure and biomarker concentrations, and about the link between biomarker concentrations and health outcomes. Table 1 provides a summary of half-life, distribution, and transport in the body.

## *Discussion & Summary*

Gallium exposure is increasing, especially in occupational settings, and environmental exposure may be of concern in close proximity to industries such as mining and smelting, coal combustion, and semiconductor manufacture. Animal studies, and gallium's use as a chemotherapeutic agent suggest significant toxicity. However, further information about human exposure are needed, including linking exposure to biomarker concentrations, and relating these two to health outcomes. Additionally, low level and chronic exposures are poorly understood, as is the role that chemical and physical form plays in determining toxicity. Gallium's basic environmental behavior is also largely unknown. It is important to remember that a lack of regulation does not imply a lack of toxicity. As with indium, because toxicity is still not well understood, care should be taken to monitor and minimize exposure through the use of good laboratory and occupational practices and use of personal protective equipment, not only in the known situations of exposure cited above, but in any situation dealing with gallium.

# **Conclusions**

We have provided a brief review of the basic chemistry, changing environmental concentrations, potential for exposure, and known health effects of indium and gallium, two important metals in electronics and new energy technologies. Due to the rapid growth in use of these metals, knowledge of their toxicities and human exposure has lagged behind their use. We hope this review stimulates further research into how workers are exposed to these metals, the relationship between these exposures and biomarkers, and the resulting health outcomes. Additionally, an evaluation of possible environmental exposures, and the effects of low level and chronic exposure to these metals is prudent. Lastly, in order to gain a true understanding of both exposure potential and health impacts, we must have a better understanding of the basic chemistry and behavior of these metals. Until we better understand the health impacts of these important metals, and until government regulations catch up to this knowledge, care should be taken whenever exposure is possible.

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# **Compliance with Ethics Guidelines**

**Conflict of Interest**

Sarah Jane O. White and James P. Shine declare that they have no conflict of interest.

# **Human and Animal Rights and Informed Consent**

This article does not contain any studies with human or animal subjects performed by any of the authors.

# **References**

Papers of particular interest, published recently, have been highlighted as: •Of importance ••Of outstanding importance

- (1) US Geological Survey, 2014, Indium Statistics, T. D. Kelly and G. R. Matos, comps., in Historical statistics for mineral and material commodities in the United States (Indium; 2014 version): U.S. Geological Survey Data Series 140, accessed 2016 at [http://minerals.usgs.gov/minerals/pubs/historical-statistics/.](http://minerals.usgs.gov/minerals/pubs/historical-statistics/) Available online at [http://minerals.usgs.gov/ds/2005/140/.](http://minerals.usgs.gov/ds/2005/140/)
- (2) US Geological Survey, 2014, Indium Statistics, T. D. Kelly and G. R. Matos, comps., in Historical statistics for mineral and material commodities in the United States (Gallium; 2014 version): U.S. Geological Survey Data Series 140, accessed 2016 at [http://minerals.usgs.gov/minerals/pubs/historical-statistics/.](http://minerals.usgs.gov/minerals/pubs/historical-statistics/) Available online at [http://minerals.usgs.gov/ds/2005/140/.](http://minerals.usgs.gov/ds/2005/140/)
- (3) Heacock, M.; Kelly, C. B.; Asante, K. A.; Birnbaum, L. S.; Bergman, A. L.; Brune, M.; Buka, I.; Carpenter, D. O.; Chen, A.; Huo, X.; Kamel, M.; Landrigan, P. J.; Magalini, F.; Diaz-Barriga, F.; Neira, M.; Omar, M.; Pascale, A.; Ruchirawat, M.; Sly, L.; Sly, P. D.; Van den Berg, M.; Suk, W. A. E-Waste and Harm to Vulnerable Populations: A Growing Global Problem. *Environ. Health Perspect.* **2016,** *124* (5), 550-555.
- (4) Wood, S. A.; Samson, I. M. The aqueous geochemistry of gallium, germanium, indium and scandium. *Ore Geol. Rev.* **2006,** *28* (1), 57-102.
- (5) Martell, A. E.; Smith, R. M. *Critical stability constants;* Plenum Press: New York, 1977.
- (6)• White, S. J. O.; Hemond, H. F. The Anthrobiogeochemical Cycle of Indium: A Review of the Natural and Anthropogenic Cycling of Indium in the Environment. *Critical Reviews in Environmental Science & Technology* **2012,** *42*, 155-186.
- This review provides detailed information about the natural and human-induced cycling of indium in the environment, along with information about indium's chemistry and toxicity.
- (7) Jorgenson, J. D.; George, M. W. *Mineral Commodity Profile: Indium*; U.S. Geological Survey: Reston, VA, 2005; Open-File Report 2004-1300.
- (8) Hines, C. J.; Roberts, J. L.; Andrews, R. N.; Jackson, M. V.; Deddens, J. A. Use of and Occupational Exposure to Indium in the United States. *Journal of Occupational and Environmental Hygiene* **2013,** *10* (12), 723-733.
- (9) Lahiri, S.; Maiti, M.; Ghosh, K. Production and separation of 111In: an important radionuclide in life sciences: a mini review. *J. Radioanal. Nucl.* **2013,** *297* (3), 309-318.
- (10) Rudnick, R. L.; Gao, S. Composition of the Continental Crust. In *Treatise on Geochemistry;*  Holland, H. D., Turekian, K. K., Eds.; Elsevier/Pergamon: Amsterdam ; Boston, 2004; pp 1- 64.
- (11) Wedepohl, K. H. The Composition of the Continental-Crust. *Geochim. Cosmochim. Acta*  **1995,** *59* (7), 1217-1232.
- (12) Maenhaut, W.; Zoller, W. H. Determination of Chemical Composition of South Pole Aerosol by Instrumental Neutron-Activation Analysis. *Journal of Radioanalytical Chemistry* **1977,**  *37* (2), 637-650.
- (13) Smith, I. C.; Carson, B. L.; Hoffmeister, F. (Eds). *Trace metals in the environment: Volume 5 - Indium;* Ann Arbor Science Publishers: Ann Arbor, Mich., 1978; pp 552.
- (14) White, S. J. O.; Keach, C.; Hemond, H. F. Atmospheric Deposition of Indium in the Northeastern United States: Flux and Historical Trends. *Environ. Sci. Technol.* **2015,** *49* (21), 12705-12713.
- (15) Chen, H. W. Gallium, indium, and arsenic pollution of groundwater from a semiconductor manufacturing area of Taiwan. *Bull. Environ. Contam. Toxicol.* **2006,** *77* (2), 289-296.
- (16) White, S. J. O.; Hussain, F. A.; Hemond, H. F.; Sacco, S. A.; Shine, J. P.; Runkel, R. L.; Walton-Day, K.; Kimball, B. The precipitation of indium at elevated pH in a stream influenced by acid-mine drainage. *Science of the Total Environment* **2016, in press,** .
- (17)• Cummings, K. J.; Virji, M. A.; Park, J. Y.; Stanton, M. L.; Edwards, N. T.; Trapnell, B. C.; Carey, B.; Stefaniak, A. B.; Kreiss, K. Respirable indium exposures, plasma indium, and respiratory health among indium-tin oxide (ITO) workers. *Am. J. Ind. Med.* **2016,** *59* (7), 522-531.
- This is a follow up study to other important studies by Cummings et al. that clearly demonstrates a link between exposure to indium particles, blood plasma concentrations, and health outcomes.
- (18) Chen, H. -. Exposure and health risk of gallium, indium, and arsenic from semiconductor manufacturing industry workers. *Bull. Environ. Contam. Toxicol.* **2007,** *78* (2), 113-117.
- (19) Ohkouchi, S.; Nakamura, Y.; Nakamura, H.; Asakawa, K. Indium nano-dot arrays formed by field-induced deposition with a Nano-Jet Probe for site-controlled InAs/GaAs quantum dots. *Thin Solid Films* **2004,** *464-465*, 233-236.
- (20) Sujatha Devi, P.; Chatterjee, M.; Ganguli, D. Indium tin oxide nano-particles through an emulsion technique. *Mater. Lett.* **2002,** *55* (4), 205-210.
- (21) Chen, H. Characteristics and risk assessment of trace metals in airborne particulates from a semiconductor industrial area of northern Taiwan. *Fresenius Environ. Bull.* **2007,** *16* (10), 1288-1294.
- (22) Chen, H.; Chen, W.; Chang, C.; Chuang, Y.; Lin, Y. Identifying airborne metal particles sources near an optoelectronic and semiconductor industrial park. *Atmos. Res.* **2016,** *174*, 97-105.
- (23) National Institute of Occupational Safety and Health. *NIOSH recommendations for occupational safety and health: compendium of policy documents and statements (DHHS NIOSH Publication no. 92-100);* U.S. Dept. of Health and Human Services: Cincinnati, Ohio, 1992; pp 208.
- (24) American Conference of Governmental Industrial Hygienists. *2007 TLVs and BEIs : based on the documentation of the threshold limit values for chemical substances and physical agents & biological exposure indices;* American Conference of Governmental Industrial Hygienists: Cincinnati, Ohio, 2007; pp 238.
- (25) Ministry of Health, Labor, and Welfare (MHLW). Technical guidelines for preventing health impairment of workers engaged in the indium tin oxide handling process. *Tokyo: Government of Japan* **2010,** .
- (26) Cummings, K. J.; Nakano, M.; Omae, K.; Takeuchi, K.; Chonan, T.; Xiao, Y.; Harley, R. A.; Roggli, V. L.; Hebisawa, A.; Tallaksen, R. J.; Trapnell, B. C.; Day, G. A.; Saito, R.; Stanton, M. L.; Suarthana, E.; Kreiss, K. Indium Lung Disease. *Chest* **2012,** *141* (6), 1512-1521.
- (27) Cummings, K. J.; Suarthana, E.; Edwards, N.; Liang, X.; Stanton, M. L.; Day, G. A.; Saito, R.; Kreiss, K. Serial evaluations at an indium-tin oxide production facility. *Am. J. Ind. Med.*  **2013,** *56* (3), 300-307.
- (28) Chonan, T.; Taguchi, O.; Omae, K. Interstitial pulmonary disorders in indium-processing workers. *European Respiratory Journal* **2007,** *29* (2), 317-324.
- (29) Hamaguchi, T.; Omae, K.; Takebayashi, T.; Kikuchi, Y.; Yoshioka, N.; Nishiwaki, Y.; Tanaka, A.; Hirata, M.; Taguchi, O.; Chonan, T. Exposure to hardly soluble indium compounds in ITO production and recycling plants is a new risk for interstitial lung damage. *Occup. Environ. Med.* **2008,** *65* (1), 51-55.
- (30) Homma, S.; Miyamoto, A.; Sakamoto, S.; Kishi, K.; Motoi, N.; Yoshimura, K. Pulmonary fibrosis in an individual occupationally exposed to inhaled indium-tin oxide. *European Respiratory Journal* **2005,** *25* (1), 200-204.
- (31) Nakano, M.; Omae, K.; Tanaka, A.; Hirata, M.; Michikawa, T.; Kikuchi, Y.; Yoshioka, N.; Nishiwakii, Y.; Chonan, T. Causal Relationship between Indium Compound Inhalation and Effects on the Lungs. *J. Occup. Health* **2009,** *51* (6), 513-521.
- (32) Homma, T.; Ueno, T.; Sekizawa, K.; Tanaka, A.; Hirata, M. Interstitial pneumonia developed in a worker dealing with particles containing indium-tin oxide. *Journal of Occupational Health* **2003,** *45* (3), 137-139.
- (33) International Agency for Research on Cancer (IARC). Indium phosphide. *IARC Monogr Eval Carcinog Risks Hum* **2006,** *86*, 197-224.
- (34) Gottschling, B. C.; Maronpot, R. R.; Hailey, J. R.; Peddada, S.; Moomaw, C. R.; Klaunig, J. E.; Nyska, A. The role of oxidative stress in indium phosphide-induced lung carcinogenesis in rats. *Toxicological Sciences* **2001,** *64* (1), 28-40.
- (35) Morgan, D. L.; Shines, C. J.; Jeter, S. P.; Wilson, R. E.; Elwell, M. P.; Price, H. C.; Moskowitz, P. D. Acute pulmonary toxicity of copper gallium diselenide, copper indium diselenide, and cadmium telluride intratracheally instilled into rats. *Environ. Res.* **1995,** *71* (1), 16-24.
- (36) Morgan, D. L.; Shines, C. J.; Jeter, S. P.; Blazka, M. E.; Elwell, M. R.; Wilson, R. E.; Ward, S. M.; Price, H. C.; Moskowitz, P. D. Comparative Pulmonary Absorption, Distribution, and Toxicity of Copper Gallium Diselenide, Copper Indium Diselenide, and Cadmium Telluride in Sprague–Dawley Rats. *Toxicology and Applied Pharmacology,* **1997,** *147* (2), 399-410.
- (37) Tanaka, A. Toxicity of indium arsenide, gallium arsenide, and aluminium gallium arsenide. *Toxicol. Appl. Pharmacol.* **2004,** *198* (3), 405-411.
- (38) Conner, E. A.; Yamauchi, H.; Fowler, B. A. Alterations in the Heme Biosynthetic-Pathway from the III-V Semiconductor-Metal, Indium Arsenide (InAs). *Chem. Biol. Interact.* **1995,**  *96* (3), 273-285.
- (39) Conner, E. A.; Yamauchi, H.; Fowler, B. A.; Akkerman, M. Biological Indicators for Monitoring Exposure Toxicity from III-V Semiconductors. *J. Expo. Anal. Environ. Epidemiol.* **1993,** *3* (4), 431-440.
- (40) Fowler, B. A.; Conner, E. A.; Yamauchi, H. Metabolomic and proteomic biomarkers for III– V semiconductors: Chemical-specific porphyrinurias and proteinurias. *Toxicology and Applied Pharmacology* **2005,** *206* (2), 121-130.
- (41) Rocha, J. B. T.; Tuerlinckx, S. M.; Schetinger, M. R. C.; Folmer, V. Effect of Group 13 metals on porphobilinogen synthase in vitro. *Toxicol. Appl. Pharmacol.* **2004,** *200* (3), 169- 176.
- (42) Van Hulle, M.; De Cremer, K.; Vanholder, R.; Cornelis, R. In vivo distribution and fractionation of indium in rats after subcutaneous and oral administration of [In-114m]InAs. *J. Environ. Monit.* **2005,** *7* (4), 365-370.
- (43) Liu, H.; Chen, C.; Chen, G.; Lee, L.; Chen, H. Relationship between indium exposure and oxidative damage in workers in indium tin oxide production plants. *Int. Arch. Occup. Environ. Health* **2012,** *85* (4), 447-453.
- (44) Tanaka, A.; Hirata, M.; Homma, T.; Kiyohara, Y. Chronic Pulmonary Toxicity Study of Indium-Tin Oxide and Indium Oxide Following Intratracheal Instillations into the Lungs of Hamsters. *Journal of Occupational Health* **2010,** *52* (1), 14-22.
- (45) Yamauchi, H.; Takahashi, K.; Yamamura, Y.; Fowler, B. A. Metabolism of Subcutaneous Administered Indium Arsenide in the Hamster. *Toxicol. Appl. Pharmacol.* **1992,** *116* (1), 66- 70.
- (46) Castronovo, F. P.; Wagner, H. N. Comparative Toxicity and Pharmacodynamics of Ionic Indium Chloride and Hydrated Indium Oxide. *Journal of Nuclear Medicine* **1973,** *14* (9), 677-682.
- (47) Fowler, B. A. Indium. *Handbook on the Toxicology of Metals, 3rd Edition* **2007,** , 569-576.
- (48) Foley, N.; Jaskula, B. Gallium A Smart Metal. *USGS Fact Sheet 2013-3006* **2013,** .
- (49) Shiller, A. M.; Frilot, D. M. The geochemistry of gallium relative to aluminum in Californian streams. *Geochimica et Cosmochimica Acta,* **1996,** *60* (8), 1323-1328.
- (50) Shiller, A. M. Dissolved gallium in the Atlantic Ocean. *Mar. Chem.* **1998,** *61* (1-2), 87-99.
- (51) Shiller, A. M.; Bairamadgi, G. R. Dissolved gallium in the northwest Pacific and the south and central Atlantic Oceans: Implications for aeolian Fe input and a reconsideration of profiles. *Geochemistry Geophysics Geosystems* **2006,** *7*.
- (52) Orians, K. J.; Bruland, K. W. The marine geochemistry of dissolved gallium: A comparison with dissolved aluminum. *Geochimica et Cosmochimica Acta,* **1988,** *52* (12), 2955-2962.
- (53) Staff, K.; Brown, M. B.; Chilcott, R. P.; Hider, R. C.; Jones, S. A.; Kong, X. L. Ga(III) complexes-The effect of metal coordination on potential systemic absorption after topical exposure. *Toxicol. Lett.* **2011,** *202* (3), 155-160.
- (54) Kawaguchi, H.; Shimizu, T.; Shirakashi, T.; Shijo, Y. Determination of ultratrace gallium in river water by electrothermal atomic absorption spectrometry after preconcentration with solvent extraction and back extraction. *Bull. Chem. Soc. Jpn.* **1998,** *71* (3), 647-650.
- (55) Deis, L. F. (Ed). *CRC handbook of chemistry and physics (89th edition) ;* CRC Press: Cleveland, Ohio, 2009;.
- (56) Geiger, F.; Busse, C. A.; Loehrke, R. I. The Vapor-Pressure of Indium, Silver, Gallium, Copper, Tin, and Gold between 0.1-Bar and 3.0-Bar. *Int. J. Thermophys.* **1987,** *8* (4), 425- 436.
- (57) Jaskula, B. W. *Gallium: Mineral Commodity Summaries*; US Geological Survey: 2016.
- (58)• Chitambar, C. R. Medical Applications and Toxicities of Gallium Compounds. *Int. J. Environ. Res. Public Health* **2010,** *7* (5), 2337-2361.
- This is a thorough review of the uses of gallium in medicine, as a chemotherapeutic, and known toxicities.
- (59) Fowler, B. A.; Sexton, M. J. Gallium and Semiconductor Compounds. *Handbook on the Toxicology of Metals, 3rd Edition* **2007,** , 547-555.
- (60) Rzhepishevska, O.; Ekstrand-Hammarstrom, B.; Popp, M.; Bjorn, E.; Bucht, A.; Sjostedt, A.; Antti, H.; Ramstedt, M. The Antibacterial Activity of Ga3+ Is Influenced by Ligand Complexation as Well as the Bacterial Carbon Source. *Antimicrob. Agents Chemother.*  **2011,** *55* (12), 5568-5580.
- (61) Lovik, A. N.; Restrepo, E.; Muller, D. B. The Global Anthropogenic Gallium System: Determinants of Demand, Supply and Efficiency Improvements. *Environ. Sci. Technol.*  **2015,** *49* (9), 5704-5712.
- (62) BURTON, J.; CULKIN, F.; RILEY, J. The Abundances of Gallium and Germanium in Terrestrial Materials. *Geochim. Cosmochim. Acta* **1959,** *16* (1-3), 151-180.
- (63) Orians, K. J.; Bruland, K. W. Dissolved Gallium in the Open Ocean. *Nature* **1988,** *332* (6166), 717-719.
- (64) McAlister, J.; Orians, K. Calculation of river-seawater endmembers and differential trace metal scavenging in the Columbia River plume. *Estuarine Coastal and Shelf Science* **2012,**  *99*, 31-41.
- (65) McAlister, J. A.; Orians, K. J. Dissolved gallium in the Beaufort Sea of the Western Arctic Ocean: A GEOTRACES cruise in the International Polar Year. *Mar. Chem.* **2015,** *177*, 101- 109.
- (66) Parker, C. E.; Brown, M. T.; Bruland, K. W. Scandium in the open ocean: A comparison with other group 3 trivalent metals. *Geophys. Res. Lett.* **2016,** *43* (6), 2758-2764.
- (67) Qin, S.; Sun, Y.; Li, Y.; Wang, J.; Zhao, C.; Gao, K. Coal deposits as promising alternative sources for gallium. *Earth-Sci. Rev.* **2015,** *150*, 95-101.
- (68) Karlsson, S.; Duker, A.; Grahn, E. Sediment chronologies of As, Bi, and Ga in Sweden impact of industrialisation. *J. Environ. Sci. Health Part A-Toxic/Hazard. Subst. Environ. Eng.* **2007,** *42* (2), 155-164.
- (69) Ames, M. R.; Gullu, G.; Beal, J.; Olmez, I. Receptor modeling for elemental source contributions to fine aerosols in New York State. *J. Air Waste Manage. Assoc.* **2000,** *50* (5), 881-887.
- (70) International Agency for Research on Cancer (IARC). Gallium arsenide. *IARC Monogr Eval Carcinog Risks Hum* **2006,** *86*, 163-196.
- (71) Liao, Y.; Hwang, L.; Kao, J.; Yiin, S.; Lin, S.; Lin, C.; Lin, Y.; Aw, T. Lipid peroxidation in workers exposed to aluminium, gallium, indium, arsenic, and antimony in the optoelectronic industry. *Journal of Occupational and Environmental Medicine* **2006,** *48* (8), 789-793.
- (72) Meigs, J. W. Gallium Fluoride Poisoning: A Probable Case with Skin Effects and Neurological Sequelae. *Journal of Occupational and Environmental Medicine* **1972,** *14* (12), 925-926.
- (73) Ivanoff, C. S.; Ivanoff, A. E.; Hottel, T. L. Gallium poisoning: A rare case report. *Food and Chemical Toxicology* **2012,** *50* (2), 212-215.
- (74) National Center for Biotechnology Information, comps., in PubChem Compound Database; CID=7963, datasheet=lcss . Available online at<https://pubchem.ncbi.nlm.nih.gov/compound/7963#datasheet=lcss> (accessed Sept. 9, 2016).
- (75) WARRELL, R.; MURPHY, W.; SCHULMAN, P.; ODWYER, P.; HELLER, G. A Randomized Double-Blind-Study of Gallium Nitrate Compared with Etidronate for Acute Control of Cancer-Related Hypercalcemia. *Journal of Clinical Oncology* **1991,** *9* (8), 1467- 1475.
- (76) Zojer, N.; Keck, A.; Pecherstorfer, M. Comparative tolerability of drug therapies for hypercalcaemia of malignancy. *Drug Safety* **1999,** *21* (5), 389-406.
- (77) FOWLER, B.; YAMAUCHI, H.; CONNER, E.; AKKERMAN, M. Cancer Risks for Humans from Exposure to the Semiconductor Metals. *Scandinavian Journal of Work Environment & Health* **1993,** *19*, 101-103.
- (78) Tanaka, A.; Hirata, M.; Shiratani, M.; Koga, K.; Kiyohara, Y. Subacute Pulmonary Toxicity of Copper Indium Gallium Diselenide Following Intratracheal Instillations into the Lungs of Rats. *Journal of Occupational Health* **2012,** *54* (3), 187-195.

(79) Liao, Y.; Yu, H.; Ho, C.; Wu, M.; Yang, C.; Chen, J.; Chang, C. Biological monitoring of exposures to aluminium, gallium, indium, arsenic, and antimony in optoelectronic industry workers. *Journal of Occupational and Environmental Medicine* **2004,** *46* (9), 931-936.

	Indium	<b>Gallium</b>
Half-life in the body	Range:	Minutes to days <sup>6</sup>
	Minutes to days (oral and	
	intravenous administration	
	in animals) $1$	
	Years (inhalation by	
	humans, intratracheal	
	administration in hamsters) <sup>2</sup>	
Distribution in the body	Lungs, kidney, liver, spleen,	Liver, bone, bone marrow,
	reticuloendothelial system <sup>3</sup>	spleen, kidneys <sup>6</sup>
Transport in the body	In blood, bound to	In blood, bound by
	transferrin $4$	transferrin $6$
<b>Biomarkers</b>	Blood serum or plasma <sup>5</sup>	Blood and urine'

Table 1. Select biological properties of indium and gallium

<sup>1</sup> Yamauchi et al. 1992; Van Hulle et al. 2005, Castronovo & Wagner 1973, Fowler 2007 and references therein

 $^2$  Cummings et al. 2016; Chonan et al. 2007; Nakano et al. 2009; Tanaka et al. 2010

 $3$  Cummings et al. 2012; Fowler 2007 and references therein

4 Fowler 2007

<sup>5</sup> Cummings et al. 2016<br><sup>6</sup> Fowler & Sexton 2007 and references therein<br><sup>7</sup> Liao et al. 2004; Liao et al. 2006; Chen 2007