# Indium and compounds

| CAS number: | 7440-74-6 (elemental) |
| --- | --- |
| Synonyms: | — |
| Chemical formula: | In |
| Structural formula: | — |

Workplace exposure standard (interim)

| TWA: | **Indium and compounds (except indium phosphide): 0.1 mg/m3 (as In)**  **Indium phosphide: 0.3 µg/m3 (as In)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **—** |
| IDLH: | **—** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.1 mg/m3 is recommended for indium and compounds (excluding indium phosphide) to protect for adverse pulmonary effects, skeletal and gastrointestinal disorders in exposed workers.

A TWA of 0.3 µg/m3 is recommended for indium phosphide to protect for cancer in exposed workers.

Given the differences in critical endpoints for indium phosphide and other indium compounds and the limited information in the available source material, a priority review of additional sources is recommended at the next scheduled review.

## Discussion and conclusions

Indium and its compounds are used in a variety of alloys and electronic applications including semiconductors and bearings in heavy machinery.

Critical effects of exposure to indium and indium compounds are pulmonary oedema, alveolar proteinosis and skeletal and gastrointestinal (GIT) disorders (ACGIH, 2018). The toxicity of individual compounds varies depending on their composition and solubility, which complicates a grouped assessment. Indium phosphide has been shown to additionally possess carcinogenic activity (DFG, 2004).

Available inhalational toxicity data are limited. Tooth decay, joint and bone pain, nervous system, GIT disorders and heart pain are reported in indium production workers but no details on exposures are available (ACGIH, 2018). In rats, exposure to indium oxide caused pulmonary oedema above 27 mg/m3 (ACGIH, 2018) and alveolar proteinosis and inflammation at 0.1 mg/m3 (ECHA, 2019).

Due to the uncertainty in the database, the current TWA of 0.1 mg/m3 is retained in the interim for indium and compounds (excluding indium phosphide). This TWA is supported by the recommendation of ACGIH (2018) and is expected to be sufficiently low to protect for the critical effects. A broader review of the available data is recommended for subsequent evaluations to identify human inhalational exposures and other indium compounds. The suitability of a grouped evaluation should also be examined as individual assessments of selected indium compounds/classes have been presented (DFG, 2004; ECHA, 2019; NICNAS, 2016).

A LOAEC of 0.03 mg/m3 for tumorigenicity, inflammation, interstitial fibrosis and proteinosis is reported for indium phosphide in a two-year inhalational study in rats and mice (DFG, 2004; IARC, 2006). Increased expression of inflammatory response proteins in the lungs of rats is also reported at 0.03 mg/m3 after three months (DFG, 2004).

TWA of 0.3 µg/m3 was derived for indium phosphide based on the LOAEC of 0.03 mg/m3 and applying two uncertainty factors of 10 each to account for the lack of a NOAEC and inter- and intra-species variation. This interim TWA is expected to protect for cancer outcomes in exposed workers.

However, a review of additional data sources is recommended at the next scheduled review of the workplace exposure standards.

## Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) except for indium phosphide, which is classified as a category 1B carcinogen.

Not classified as a skin sensitiser or respiratory sensitiser according to the GHS.

A skin notation is not warranted based on the available evidence.

# Appendix

### Primary sources with reports

| Source Year set Standard |
| --- |
| SWA 1991 TWA: 0.1 mg/m3 | |
|  |
| ACGIH 2001 TLV-TWA: 0.1 mg/m3 as In |
| TLV-TWA intended to minimise potential for pulmonary oedema, acute pneumonitis and potential skeletal and GIT disorders; derivation not detailed.  Summary of data:  Severity and nature of toxic response depends on the specific indium compound. Elemental In, indium sesquioxide (In2O3) and indium sulfate (In2[SO4]3) are the most industrially common/important compounds.  TLV-TWA based on weight of evidence that suggests 0.1 mg/m3 (as In) is sufficiently low to protect for principal critical effects of adverse skeletal and GIT effects and pulmonary oedema. TLV-TWA derivation not discussed.  Human data:   * Indium production workers suffered tooth decay, joint and bone pain, nervous system and GIT disorders and heart pain (exposure durations and concentrations not specified).   Animal data:   * Oral dose of In2O3 10,000 mg/kg lethal to mice:   + other administration routes and soluble salts are much more toxic   + <1 mg/kg lethal to rabbits (parenteral route and soluble salt not specified) * Soluble salts are very irritating to eyes (no further details provided) * Granular alveolar oedema at 24–97 mg/m3 in repeat inhalation study with In2O3 (rats, 224 h total exposure, duration and frequency not specified):   + healing process during 12 wk observation period did not cause fibrosis   + alveolar proteinosis still present and resulted in reduced alveolar clearance * High incidence of malformed digits in developmental study with iv injected indium nitrate (hamsters, GD 8):   + total embryopathy at doses >1 mg/kg   + relevance of study to workplace exposures questioned by the agency due to administration route and undocumented effects on maternal toxicity * Intestinal absorption of oral doses is very low   + 0.2–0.4% absorbed, rest excreted in faeces (rats) * No mutagenicity data presented.   Insufficient data to recommend a TLV-STEL or notations for carcinogenicity, skin absorption or sensitisation. |
| DFG 2004 Not established |
| Summary of additional data:  No grouped assessment of indium and its compounds available; only an assessment of indium phosphide (InP) is presented.  MAK not established for InP due to demonstrated carcinogenicity in repeat inhalation study with rats and mice; insufficient evidence for classification as a genotoxic carcinogen.  Insufficient evidence for skin and sensitiser notations.  Human data:   * None presented.   Animal data:   * Carcinogenic effect of InP likely due to generation of excess ROS   + increased expression of inflammatory response proteins in lungs at 0.03 mg/m3 InP after 3 mo during a 2-yr chronic inhalation study (rats) * Majority of intratracheally applied dose of 10 mg/kg present in lungs after 14 d (rats); <0.36% distributed to other organs:   + lung clearance half-life: 144–163 d (mice), 262–291 d (rats); dose-independent * Repeat inhalation study with treatment groups 0, 1, 3, 10, 30, and 100 mg/m3 (rats, mice, 5 h/d, 5–7 d/wk, 14 wk):   + grey discoloration and 2.7–4.4-fold increase in lung weights in all exposure groups (unclear if dose-dependent)   + chronic inflammation in lungs and associated lymph nodes at 30–100 mg/m3   + haematopoietic cell proliferation and liver cell necrosis at 10 mg/m3   + no changes to reproduction or fertility noted * Similar pathologies to 14-wk study were reported in chronic inhalation study with treatment groups 0, 0.03 mg/m3 for 2 yr and 0.1, and 0.3 mg/m3 for 22 wk (rats, mice, 6 h/d, 5 d/wk):   + lung weights were 1.6–2.1 (rats) and 1.7–2 (mice) times heavier than controls at 0.1‑0.3 mg/m3   + lung damage corresponded qualitatively to that observed in 14-wk study, but less severe (no further details)   + lung clearance half-times was dose-independent, based on a deposition and clearance model, lowest total exposure group calculated to be 0.1 mg/m3 group, followed by 0.03 mg/m3 and 0.3 mg/m3 in both rats and mice   + 0.1 and 0.3 mg/m3 groups exposed for 22 wk and observed for 2 yr due to mortality, low dose group exposed for full 2 yr, survival rates as follows;     - mice: 43–66% at 0.1–0.3 mg/m3, 26–48% at 0.03 mg/m3, 74–86% in controls     - rats: 52–72% at 0.1–0.3 mg/m3, 58–63% at 0.03 mg/m3, 54–68% in controls   + in rats, increased incidences of lung adenomas and carcinomas (12–52%) and adrenal tumours (37–52%) in all treatment groups compared to controls (2 and 20%, respectively), dose dependency not discussed   + accumulation in testes up to 112 d post-exposure (male rats)   + LOAEC: 0.03 mg/m3 for tumorigenicity, chronic inflammation, interstitial fibrosis, and proteinosis * No signs of foetal toxicity in developmental inhalation study at 1–10 mg/m3 (rats, mice, GD 4–19, exposure duration not specified); maternally toxic effects consistent with other inhalational studies at those concentrations * Equivocal evidence from *in vivo* genotoxicity evaluation due to potentially confounding observations at severely toxic exposures; 30 mg/m3 (rats, 5 h/d, 5–7 d/wk,14 wk). |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN NA NA |
| No report. |

### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| HSE |  | 2002 | * 8 h TWA: 0.1 mg/m3; 15 min STEL: 0.3 mg/m3. |
| NICNAS |  | 2016 | *Indium phosphide:*   * Grouped in carcinogenic, mutagenic, and/or reproductive toxicants (CMRs) * Not listed as genotoxic but considered carcinogenic based on positive results of 2-yr inhalation study and potentially damaging to fertility based on InP accumulation in testes in 14 wk study both cited in DFG (2004). |
| IARC |  | 2006 | *Insoluble indium compounds:*   * Higher indium serum, blood and urine levels in workers (n=107) exposed to insoluble indium-containing particulates (not specified) than unexposed workers (n=24).   *Indium phosphide:*   * Probably carcinogenic to humans (Group 2A) based on high incidences of malignant lung neoplasms and liver neoplasms at 0.03–0.3 mg/m3 (rats, mice, 22 wk–2 yr, also cited by DFG, 2004).   *Indium trichloride:*   * Retained in lungs for up to 56 d after intratracheal instillation despite solubility of the compound. |
| NTP |  | 2001, 2018 | *Insoluble compounds:*   * Indium compounds not absorbed well by GIT (<2%) * Accumulation in major airways with little absorption following intratracheal injection (rodents).   *Indium phosphide:*   * Negative micronucleus results *in vivo* (mice) * Clear evidence for carcinogenicity in mice and rats in 2 yr inhalation study (0.03–0.3 mg/m3 also cited in DFG, 2004).   *Indium trichloride:*   * Negative results in bacterial *in vitro* assay * Positive results for micronucleus assay in human TK6 Cells *in vitro.* |
| ECHA |  | 2019 | *Indium (elemental):*   * Particle size distribution ≈4 µm needed for acute inhalation tests; is not technically feasible due to softness of metal * In powder is not marketed for industrial scale ≤20 µm and cannot form appreciable amount of dust * Inhalation of In metal not considered likely under workplace conditions * Dermal exposure not considered relevant to the workplace.   *Soluble indium compounds:*   * Retained in the lung and rapidly absorbed following inhalation or intratracheal instillation; half-life ≈1 h.   *Insoluble indium compounds:*   * Alveolar proteinosis and hyperplasia, and lung inflammation in sub-chronic inhalation study at 0.1–1 mg/m3 of In2O3 (rats, 6 h/d, 5 d/wk, 13 wk):   + dose-related increase of indium in blood and lungs   + particles were deposited in the lung, and regional lymph nodes   + study used as basis for DNEL of 0.0063 mg/m3 * In2O3 absorbed slowly; half-life ≈2 mo. |

### Carcinogenicity — non-threshold based genotoxic carcinogens

| Is the chemical mutagenic? | No |
| --- | --- |
| **The chemical is not a non-threshold based genotoxic carcinogen.** |  |

## Notations

| Source | Notations |
| --- | --- |
| SWA | — |
| HCIS | *Indium phosphide*: Carcinogenicity – category 1B  *All* *other* *compounds*: NA |
| NICNAS | *Indium phosphide*: Carc. 1B  *All* *other* *compounds*: NA |
| EU Annex | *Indium phosphide*: Carcinogenicity – category 1B  *All* *other* *compounds*: NA |
| ECHA | *Indium*: — |
| ACGIH | *All* *compounds*: — |
| DFG | *Indium* *phosphide*: Carcinogenicity – 2 |
| SCOEL | NA |
| HCOTN | NA |
| IARC | *Indium* *phosphide*: Carcinogenicity – Group 2A |
| US NIOSH | NA |

NA = not applicable (a recommendation has not been made by this Agency); — = the Agency has assessed available data for this chemical but has not recommended any notations

### Skin notation assessment

| Calculation |
| --- |
| Insufficient data to assign a skin notation. |

### IDLH

| Is there a suitable IDLH value available? | No |
| --- | --- |

## Additional information

| Molecular weight: | 114.82 (elemental) |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa: | 1 ppm = Number mg/m3; 1 mg/m3 = Number ppm |
| This chemical is used as a pesticide: |  |
| This chemical is a biological product: |  |
| This chemical is a by-product of a process: |  |
| A biological exposure index has been recommended by these agencies: | ACGIH  DFG  SCOEL |

## Workplace exposure standard history

| Year | Standard |
| --- | --- |
| Click here to enter year |  |

## References

American Conference of Industrial Hygienists (ACGIH®) (2018) TLVs® and BEIs® with 7th Edition Documentation, CD-ROM, Single User Version. Copyright 2018. Reprinted with permission. See the [*TLVs® and BEIs® Guidelines section*](http://www.acgih.org/tlv-bei-guidelines/policies-procedures-presentations) on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2004) Indiumphosphid – MAK value documentation, German language edition.

European Chemicals Agency (ECHA) (2019) Indium – REACH assessment.

IARC (2006) Cobalt in Hard Metals and Cobalt Sulfate, Gallium Arsenide, Indium Phosphide and Vanadium Pentoxide, volume 86.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) CMR chemicals not registered under REACH: Human health tier II assessment – IMAP report.

National Toxicology Program (NTP) (2001) Technical Report on the Toxicology and Carcinogenesis Studies of Indium Phosphide (CAS No. 22398-80-7) in F344/N Rats and B6C3F1 Mice (Inhalation Studies). NTP Toxicity report series No. 499. DHHS (NIH) Pub No 01-4433.

National Toxicology Program (NTP) (2018) Indium (III) chloride (10025-82-8) Chemical Effects in Biological Systems (CEBS).

National Toxicology Program (NTP) (2018) Indium phosphide (22398-80-7) Chemical Effects in Biological Systems (CEBS).

Tenth Adaptation to Technical Progress Commission Regulation (EU Annex) No 2017/776 amending, for the purposes of its adaptation to technical and scientific progress, Regulation (EC) No 1272/2008 of the European Parliament and of the Council on classification, labelling and packaging of substances and mixtures (the CLP Regulation).