# Isocyanates, (POLY-) (as-NCO)

| CAS number: | TDI: 584-84-9  2,6-TDI: 91-08-7  HDI: 822-06-0  IPDI: 4098-71-9  MDI: 101-68-8  HMDI 5124-30-1 |
| --- | --- |
| Synonyms: | TDI: Toluene-2,4-diisocyanate, 2,4-Diisocyanatotoluene, 2,4-TDI  2,6-TDI: Toluene-2,6-diisocyanate  HDI: Hexamethylene diisocyanate, 1,6-Diisocyanatohexane  IPDI: Isophorone diisocyanate  MDI: Methylenebisphenyl isocyanate  HMDI: Dicyclohexylmethane 4,4'-diisocyanate, 4,4'-methylenedicyclohexyl diisocyanate, Methylene bis(4 -cyclohexylisocyanate) |
| Chemical formula: | — |
| Structural formula: | — |

Workplace exposure standard (interim)

| TWA: | **0.0001 mg/m3 as NCO** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **—** |
| Notations: | **Sk., DSEN, RSEN** |
| IDLH: | **2.5 ppm (TDI)**  **75 mg/m3 (MDI)** |
| **Sampling and analysis:** The recommended value is quantifiable through available sampling and analysis techniques. | |

## Recommendation and basis for workplace exposure standard

A TWA of 0.0001 mg/m3, as NCO, is recommended to reduce the risk of occupational asthma and to protect for irritation of the eyes and mucous membranes in exposed workers.

A priority in-depth assessment of the toxicological and epidemiological data for the group of chemicals are recommended.

## Discussion and conclusions

In this evaluation, the term ‘isocyanates’ has been used for those compounds that possess either 2 (diisocyanates) or 3 (triisocyanates) functional groups, sometimes called polyisocyanates. Monoisocyanates are not subject of this report.

Isocyanates are used in many industries. They are present in external coatings and paints and are used in the production of products such as flexible and rigid foams, adhesives and sealants. In practice, mixtures of different types and different forms of isocyanates are used. The toxicology of this group is very similar with the critical effects being asthma due to sensitisation and irritation of the skin, mucous membranes, eyes and respiratory tract. There is also the potential for both irritant and allergic contact dermatitis. No difference in potency for the different polyisocyanates has been identified based on the available epidemiological data (ACGIH, 2018; HCOTN, 2018).

The ACGIH (2018) recommended the 2001 TLV-TWA (0.034 mg/m3) for toluene di-isocyanate (TDI) be applied to other polyisocyanates due to a lack of data for the latter. Confusingly, in 2016, the TLV‑TWA for TDI was reduced to 0.007 mg/m3 based on data identified in workers relating to asthma, pulmonary function and eye irritation. All recommended polyisocyanates’ TLV-TWA came with a caveat that they may not protect susceptible workers from possible sensitisation or an allergic reaction in previously sensitised individuals (ACGIH, 2018).

HCOTN (2018) acknowledged that a threshold for isocyanate-induced sensitisation and development of asthma could not be determined. HCOTN established an exposure-response relationship using data from two studies in workers exposed to hexamethylene diisocyanate (HDI) and one study of workers exposed to TDI. This was used as the basis of deriving a concentration that corresponds with an extra risk of 1% for occurrence of adverse effects of the airways characteristic of occupational asthma (OA). Using this risk-based methodology, HCOTN (2018) derived a recommended TWA value for polyisocyanates at 0.1 µg/m3 (0.0001 mg/m3) for an 8-hour working day for a reduced risk of OA.

Additionally, ACGIH (2018) reported that since the mid-1970s, annual OA incidence rates have been less than 1% against measured 8-hour workplace TDI concentrations of less than 0.035 mg/m3.

Asthma has been induced in previously sensitised subjects when challenged at 0.007 mg/m³ TDI. In controlled experiments, sensitisation of participants not suffering from OA, occurred at 0.07 mg/m³ (NICNAS, 2013).

A TWA of 0.1 µg/m3 (0.0001 mg/m3) (as – NCO) by HCOTN (2018) is recommended in the interim for polyisocyanates given that polyisocyanates exist as mixtures in the workplace, the toxicology of this group is very similar with the critical effects being sensitisation related and the concentrations of TDI at 0.007 mg/m3 may not sufficiently protect for sensitisation.

A priority in-depth assessment of the toxicological and epidemiological data for the chemical is recommended due to residual uncertainty regarding toxicological difference of the individual poly-isocyanate compounds.

## Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS).

Classified as a skin sensitiser and respiratory sensitiser according to the GHS.

A skin notation is warranted based on evidence of systemic effects in humans following dermal contact.

# Appendix

### Primary sources with reports

| **Source Year set Standard** |
| --- |
| SWA 1990 TWA: 0.02 mg/m3; STEL: 0.07 mg/m3 | |
| * TWA and STEL for Isocyanates, all, (as -NCO) * Adopted ACGIH (1986) supported by HSE (1987) evidence * Isocyanate prepolymer aerosols have the same ability as the monomer vapours to cause adverse respiratory effects and sensitisations. |
| ACGIH 2001 TLV-TWA 0.005 ppm (0.034 mg/m3) (HDI, IPDI, MDI, HMDI)  ***2016***  ***TLV-TWA: 0.001 ppm (0.007 mg/m3); TLV-STEL: 0.005 ppm***  ***(0.035 mg/m3) (TDI)*** |
| **HDI – Hexamethylene diisocyanate**  TLV-TWA recommended to minimise the potential eye, nose and respiratory tract irritation and possible pulmonary sensitisation.  Recommends the 2001 TLV–TWA of 0.005 ppm for TDI be applied to HDI until more information specific to HDI becomes available  The recommended TLV may not protect susceptible workers from possible sensitisation or an allergic reaction in previously sensitised individuals  Summary of data:   |  |  |  |  | | --- | --- | --- | --- | |  | Exposure Information | Effects/Outcomes/Symptoms | Notes | | TLV-TWA | 0.005 ppm (0.034 mg/m3) | Toxicology of HDI is like TDI; The 2001 TDI TLV-TWA has been adopted until more information becomes available. | May not protect for sensitisation | | Limited study in 82 workers | <0.014 ppm (0.001 mg/m3)  No duration provided | All workers complained of irritation of eye and upper respiratory tract | Co-exposure to phosgene and chlorobenzene likely to cause of complaint | | Workers potentially exposed | ≤0.04 ppm (0.28 mg/m3)  No duration provided | Normal pulmonary function measurements. Workers complained of eye, nose and throat irritation; cough; and chest discomfort | Likely co-exposures to other chemicals | | 3 subjects with occupational asthma | Given HDI challenge doses | 1 experienced early reaction; 2 subjects had late asthmatic responses; FEV1 was reduced from 13% to 31%, 6 to 8 hours after the specific challenge |  |  * No animal data presented * Adequate HDI exposure information is not available to support a TLV * The existing information indicates that the toxicological action of HDI is like that of TDI, with eye and respiratory tract irritation and possible pulmonary sensitisation * 2001 TDI TLV-TWA has been adopted by ACGIH until more information becomes available.   The recommended TLV may not protect susceptible workers from possible sensitisation or an allergic reaction in previously sensitised individuals.  **IPDI – Isophorone diisocyanate**  Recommends the 2001 TLV–TWA of 0.005 ppm for TDI be applied to IPDI until more information specific to IPDI becomes available  The recommended TLV may not protect susceptible workers from possible sensitisation or an allergic reaction in previously sensitised individuals  Summary of data:   |  |  |  |  | | --- | --- | --- | --- | |  | Exposure Information | Effects/Outcomes/ Symptoms | Notes | | TLV-TWA | 0.005 ppm (0.034 mg/m3) | In absence of quantitative data, the 2001 TLV-TWA for TDI is applied | Reported skin sensitisation, asthma and allergic dermatitis for IPDI exposed workers warrant consideration of a sensitiser (SEN) notation  TLV-TWA may not protect for sensitisation | | Skin sensitisation reported following exposure | Patch test | Four sensitised workers were patch tested with IPDI and the results of these challenge tests were found to be strongly positive. The control subjects were negative |  | | Skin sensitisation reported following exposure | A single 1-hr workplace exposure to IPDI  No further information | Caused eczema in 3 of 4 workers |  | | Asthma | Workplace exposure to paint containing IPDI  Unspecified exposure information | 50-year-old spray painter developed severe asthma soon after the introduction of a new paint containing IPDI; Positive results in bronchial challenge test of spray painter |  | |  | Workplace exposure to paint containing IPDI | Symptoms of chest tightness and dyspnoea reported in automobile spray painter using paint containing IPDI |  | | Animal data: LC50 | 33 mg/m3 (rats, 4 h/d for 5 d) |  |  | |  |  | Moderate skin and eye irritation in rabbits |  | |  |  | Moderate skin sensitisation in guinea pigs | Consideration of a sensitiser notation is warranted, however insufficient data to recommend a skin, sensitiser or carcinogenicity notation |   **MDI – Methylenebisphenyl isocyanate**  Recommends the 2001 TLV–TWA of 0.005 ppm for TDI be applied to MDI until more information specific to MDI becomes available  The recommended TLV may not protect susceptible workers from possible sensitisation or an allergic reaction in previously sensitised individuals. The recommended TLV may not protect susceptible workers from possible sensitisation or an allergic reaction in previously sensitised individuals  **HMDI – Dicyclohexylmethane 4,4'-diisocyanate**  Recommends the 2001 TLV–TWA of 0.005 ppm for TDI be applied to HMDI until more information specific to HMDI becomes available  The recommended TLV may not protect susceptible workers from possible sensitisation or an allergic reaction in previously sensitised individuals.  **TDI (2,4- or 2,6-) or as a mixture – Toluene-2,4-diisocyanate, Toluene-2,6-diisocyanate**  TLV-TWA and TLV-STEL are derived from human data, supported by animal data, demonstrating sensitisation potential and induction of occupational asthma (OA). Workers already sensitised may not be protected.  Summary of data:  Human data:   * Recognised sensitiser following dermal absorption and/or inhalation in the workplace * TDI induced OA incidence (location unknown, assumed USA): * 5.6% in 1961–1970 corresponding to >0.02 ppm * 1.8% in 1967–1979 corresponding to 0.0034–0.01 ppm * 0.7% in 1980–1996 corresponding to 0.0003–0.0027 ppm * data suggest that efforts to control diisocyanates have reduced the number of worker OA claims * annual OA incidence rates less than 1% since the mid-1970s; when 8-h TDI concentrations <5 ppb as determined by personal monitoring * A study in 136 workers exposed at <1 ppb reported eye and lower airways irritation and nose bleeding * TLV-STEL based on: * FEV1 reductions reported in workers exposed at 0.002–0.003 ppm TDI * no consistent evidence of accelerated FEV1 loss in workers exposed up to 0.005 ppm TDI; longitudinal studies with ongoing medical surveillance.   Animal data:   * Guinea pigs exposed at ~1.3 ppm TDI, 3 h/d for 5 d; increase breathing rate as a measure of respiratory sensitisation. Challenge exposures of 18 to 46 ppb at 1-wk intervals following the 5-d exposures produced both immediate and delayed-type hypersensitivity * Ability to cause respiratory hypersensitivity following dermal exposure: no further information * Rats and mice exposed via inhalation at up to 0.15 ppm; 6 h/d, 5 d/wk, 110 wk; no increase in tumours * Oral gavage exposures of mice (105 wk) and rats (106 wk) produced an increase in tumours at multiple sites; likely to be a consequence of the toluene diamines formed from TDI in the acidic environment of the gastrointestinal tract; not relevant to occupational exposure. |
| DFG 2013 Hexamethylene diisocyanate  MAK: 0.005 ppm (0.035 mg/m3)  Momentary Value 0.01 ppm (0.07 mg/m3)  ***Diisocyanate Grouping***  ***MAK:* TWA 0.01 ppm**  **IPDI (0.09 mg/m3),MDI (0.1 mg/m3),**  **NDI (0.09 mg/m3), TDI (0.07 mg/m3)** |
| Two MAK value documents dated 2013 have been sourced:   1. Hexamethylene diisocyanate 2. Diisocyanates including HDI   It is not clear why HDI has been recommended in two different MAK values, but it appears the stand-alone MAK applies at this point.  **Hexamethylene diisocyanate (HDI) - 0.005 ppm (0.035 mg/m3)**  Summary of additional data:   * MAK value reduced to 0.005 ppm; not expected to produce irritant effects: * does not apply for persons with non-specific bronchial hyperreactivity or allergic HDI hypersensitivity, as minimal HDI concentrations are already able to provoke bronchospastic condition * Short-term exposure at 0.02 ppm (0.14 mg/m3) in human volunteers;mild irritant effects in the eye; perceived by smell at this concentration; marked irritation of eye and throat at 0.1 ppm (0.7 mg/m3) (no further information) * No symptoms observed in volunteers exposed at ~0.0035 ppm (0.025 mg/m3); single exposure for 7.5 h * Epidemiological study: irritation to eye, nose and throat reported at concentrations of 0.001 mg/m3 including short-term peaks exceeding this value (no further information) * Sensitisation of the airways reported in humans * In rats: NOAEC 0.005 ppm (0.035 mg/m3) for >2 yr; slight histological changes in the nasal mucosal epithelium.   **Diisocyanates – 0.01 ppm**  **HDI (0.07 mg/m3), IPDI (0.09 mg/m3), MDI (0.1 mg/m3), TDI (0.07 mg/m3)**  Summary of additional data:   * Reported no acute decline in lung function at concentrations <20 ppb in animals; 15 wk inhalation study * Evidence from human studies indicate upper threshold limit value of 20 ppb in humans; basis for TWA * Includes reference to naphthalene diisocyanate (NDI) with a MAK of 0.09 mg/m3. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2018 TWA: 0.1 µg/m3 (0.0001 mg/m3) NCO |
| **Diisocyanates and triisocyanates (isocyanates)**  Summary of additional data:   * TWA applies for di- and triisocyanates and was derived excluding studies with exposure >100 µg/m3, as these were not considered suitable starting point to derive a value. The assessment addressed the following isomers: * toluene diisocyanate (TDI) * hexamethylene diisocyanate (HDI) * methylene diphenyl diisocyanate (MDI) * polymeric MDI (PMDI), the primary technical/ commercial form of MDI * naphthalene diisocyanate (NDI) * isophorone diisocyanate (IPDI) * HDI biuret * HDI trimer isocyanurate * Isocyanates are chemically characterised by the presence of NCO groups which have been mechanistically linked to sensitising properties * In practice, mixtures of different types and different forms of isocyanates are used. For most of these isocyanates, insufficient data are available for a quantitative hazard assessment * No identified difference in potency for different isocyanates based on the available epidemiological data * In humans, exposure to isocyanates can result in: * irritation of the skin, mucous membranes, eye and respiratory tract * asthma due to sensitisation; reported as most common * irritant and allergic contact dermatitis and hypersensitivity pneumonitis/allergic alveolitis; reported as less prevalent * A threshold for isocyanate-induced sensitisation and development of asthma cannot be determined and therefore a risk-based advisory recommended of TWA of 0.1 µg/m3 (NCO) is derived: * TWA corresponds to workers have an extra risk of 1% of bronchial hyperreactivity (BHR), compared to the general population. based primarily on information from the first 2 studies: * **study 1** (Pronk, 2007) in 581 spray painters with cumulative exposure ranging from 4–66, 464 µg/m3\*h\*mo (mean 3,682 µg/ m3\*h\*mo); statistically significant associations were found for exposure and asthmatic symptoms, COPD-like symptoms, work-related chest tightness and work-related conjunctivitis * **study 2** (Pronk, 2009) in 229 spray painters; cumulative exposure 15.4–66,464 µg/m3.h.mo-1 (mean 4,530 µg/m3.h.mo-1); statistically significant exposure-related decreased FEV1, FEV1/FVC and flow-volume parameters independent of BHR * **study 3** (support study) (Collins, 2017) in 197 TDI manufacturing workers; increased risk of TDI asthma for cumulative and peak exposures; 0.14 µg/m3 NCO for 8-h associated with 1% extra risk of TDI-induced asthma (complaints consistent with occupational asthma) * Risk calculation using data from **study 1** and **study 2**: * exposure-response analysis using exposure data on the individual level. Analyses using splines showed that the logistic model had best fit. The exposure response relationship had a regression coefficient of 0.0775 for BHR and 0.0467 for asthma (BHR and wheeze) in a logistic regression analysis. These slopes lead to exposure levels at which the extra risk is 1% of respectively 0.10 and 0.20 µg/m3 * exposure-response analysis using exposure data after categorisation. The exposure response relationship was also calculated using a simple Poisson regression analysis to model an exposure-response relationship through the origin (no intercept, at zero exposure risk equals risk in controls) relative to the baseline prevalence of BHR20 or asthma in non-exposed using the below given information. Calculations were performed by using SAS software * **study 3** wasa logistic regression analysis for the association between TDI-induced asthma and cumulative TDI exposure; peak exposures (95th percentile) and other respiratory parameters were studied * Immunological cross-reactivity between isocyanates observed and suggests a common mechanism of action * Reported skin contact with isocyanates can cause sensitisation leading to allergic asthma * At relatively high concentrations, all isocyanates are irritating to the mucous membranes of the eye and nose * Considers animal toxicity data on isocyanates of limited value for derivation of TWA value. |

### Secondary source reports relied upon

| **Source** |  | **Year** | **Additional information** |
| --- | --- | --- | --- |
| NICNAS |  | 2013 | * Reported a challenge at 1 ppb (0.007 mg/m³) TDI induces asthma in previously sensitised subjects * In controlled experiments, sensitisation of subject not suffering from OA, occurred at levels at 0.01 ppm (0.07 mg/m³). |

### 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 | Sen |
| HCIS | — |
| NICNAS | Respiratory sensitisation – category 1, Skin sensitisation – category 1 (TDI) |
| EU Annex | Skin sensitisation – category 1, Respiratory sensitisation – category 1 |
| ECHA | Resp. Sens. 1, Skin Sens. 1 |
| ACGIH | Skin, DSEN, RSEN (TDI) |
| DFG | Sh (dermal sensitiser), Sa (respiratory sensitiser) |
| SCOEL | NA |
| HCOTN | Skin, Skin sensitiser; Respiratory sensitiser |
| IARC | Carcinogenicity – Group 2B (TDI); Group 3 (MDI) |
| US NIOSH | SK: SEN (IPDI) |

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 |
| --- |
| |  |  |  |  | | --- | --- | --- | --- | | Adverse effects in human case study: | yes | 4.00 |  | | Dermal LD50 ≤1000 mg/kg: |  |  |  | | Dermal repeat-dose NOAEL ≤200 mg/kg: |  |  |  | | Dermal LD50/Inhalation LD50 <10: |  |  |  | | *In vivo* dermal absorption rate >10%: |  |  |  | | Estimated dermal exposure at WES >10%: |  |  |  | |  |  |  | **a skin notation is warranted** | |

### IDLH

| Is there a suitable IDLH value available? | Yes |
| --- | --- |

## Additional information

| Molecular weight: | Varies |
| --- | --- |
| 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.

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Deutsche Forschungsgemeinschaft (DFG) (2013 (a,b,c,d)) Diisocyanates – MAK value documentation.

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National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2014) Toluene diisocyanates: Human health tier II assessment – IMAP report

Tenth Adaptation to Technical Progress Commission Regulation (EU) 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).

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