# Trimellitic anhydride

| CAS number: | 552-30-7 |
| --- | --- |
| Synonyms: | Anhydrotrimellitic acid, TMA, TMAN,1,2,4-Benzenetricarboxylic anhydride, 1,2,4-Benzenetricarboxylic acid 1,2-anhydride, Benzene-1,2,4-tricarboxylic acid 1,2-anhydride, trimellitic acid anhydride |
| Chemical formula: | C9H4O5 |

 Workplace exposure standard (amended)

| TWA: | **0.06 ppb (0.5 µg/m3)** |
| --- | --- |
| STEL: | **—** |
| Peak limitation: | **0.02 ppb (2 µg/m3)** |
|  Notations: | **Sk., RSEN, DSEN** |
| IDLH: | **—** |
| **Sampling and analysis:** There is uncertainty regarding quantification of the recommended value with available sampling and/or analysis techniques. |

## Recommendation and basis for workplace exposure standard

A TWA of 0.06 ppb (0.5 µg/m3) is recommended to protect for respiratory and dermal sensitisation and mucous membrane irritation in exposed workers.

A peak limitation of 0.02 ppb (2 µg/m3) is recommended to protect for acute respiratory and dermal sensitisation.

## Discussion and conclusions

Trimellitic anhydride is used in the manufacture of plastics, resins, plasticisers and various coatings.

The critical effects of exposure are respiratory and dermal sensitisation and mucous membrane irritation.

Respiratory and dermal sensitisation potential, as measured by specific immunological responses, are observed in various epidemiological studies and confirmed in animal models (ACGIH, 2018). Odds ratios (OR) for both dermal and respiratory sensitisation increased in workers exposed at 10 to 40 µg/m3 (ACGIH, 2018). In another well-conducted cohort study of exposed workers, immunological diseases were associated with average exposures above 2 µg/m3 and a peak of 120 µg/m3 but not at less than 0.5 µg/m3 (ACGIH, 2018; HCOTN, 2010). However, a 9 per cent incidence of a specific immunological response was recorded at 0.5 µg/m3 (ACGIH, 2018). Respiratory sensitisation was induced following dermal application in controlled animal studies (ACGIH, 2018).

Based on the absence of immunologically mediated respiratory disease in exposed workers reported in a cohort study of exposed workers, ACGIH (2018) recommend a TWA equivalent of 0.5 µg/m3. From a dose-response relationship based on the same dataset, HCOTN (2010) estimated that exposure at 0.18 µg/m3 may be expected to increase the risk of sensitisation by 0.1 per cent but did not recommend a health-based occupational exposure limit (HBROEL). The current MAK recommendation of 0.04 mg/m3 predates the publication of this cohort study but was provisionally intended to only protect for local irritation (DFG, 1981–2000). Based on the available human exposure data, the TLV-TWA of 0.5 µg/m3 and TLV-STEL of 2 µg/m3 by ACGIH (2018) are recommended to be adopted as TWA and peak limitation by SWA. The peak limitation is recommended in favour of a STEL due to the severity of the critical effects. These are expected to be protective of respiratory and dermal sensitisation and mucous membrane irritation.

## 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 recommended as evidence indicates contact dermatitis in humans and reports of systemic effects in animals.

# Appendix

### Primary sources with reports

| Source Year set Standard  |
| --- |
| SWA 1991 TWA: 0.005 ppm (0.039 mg/m3) |
|  |
| ACGIH 2014 TLV-TWA: 0.00006 ppm (0.0005 mg/m3); TLV-STEL: 0.0002 ppm (0.002 mg/m3) (Inhalable vapor fraction) |
| TLV-TWA and TLV-STEL recommended to minimise potential for dermal and respiratory sensitisation and skin and mucous membrane irritation. RSEN and DSEN notations recommended based on positive sensitisation in humans and animals; dermal contact was demonstrated to elicit respiratory sensitisation in animals, skin notation therefore recommended.Summary of information:TLV-TWA intended to be measured as combined vapour and particulate fraction to account for potential volatile losses during sampling. TLV-TWA based on increased OR to develop dermal and respiratory sensitisation of 10 and 5.9, respectively, in workers exposed at 10–40 µg/m3­; exposures at 0.5 µg/m3 not associated with IgG disease in exposed workers, an IgG antibody response was elicited in 9% of workers at this concentration. Sensitised workers should experience improved immunologic outcomes if exposures are reduced below 4 µg/m3; though some may require complete removal from exposure.Human data:* Single exposures caused local irritation and did not induce potent immunological response (no further details provided):
* latency for sensitisation between several weeks to years
* 5% incidence of immunologically mediated disease in workers exposed at mean levels of 2 µg/m3 (peak: 120 µg/m3):
* used as justification for TLV-STEL by agency
* Increased OR for dermal and respiratory sensitisation (10 and 5.9, respectively) in workers exposed at 10–40 µg/m3 compared to those exposed at <10 µg/m3
* Exposure-dependent levels of IgG and IgG and IgE disease in workers (n=286) exposed at <0.5–130 µg/m3; incidence of IgG and IgE diseases in these workers ranged from 0–43% and 0–25%, respectively:
	+ no cases of IgG disease in workers exposed at 2.4 µg/m3 (mean: 0.5 µg/m3)
	+ 9% had IgG antibody for serum albumin adduct of substance at this concentration.

Animal data: * Lung cell adducts became sites for immunocytotoxic injury following repeat inhalation at 500 µg/m3 (rats, 4 h/d, 1–10 d)
* Immediate respiratory resistance and increased eosinophils in lungs at 150 mg/m3 (30 min) in pre-sensitised guinea pigs:
* respiratory resistance reversible in 6 h
* Haemorrhagic lung foci at 500 µg/m3 correlated well with increased Ig levels following challenge with 500 µg/m3 after 29 d (rats, 6 h/d)
* Significant increase in IgE serum levels following dermal induction with 10% solution and inhalation challenge with intranasal instillation or vice versa 17–27 d (mice)
* Dermal hypersensitivity and IgE response following dermal applications of >5% solutions followed by dermal challenge after 7 d (mice)
* NOAEC: 30 µg/m3 for respiratory sensitisation and dose-dependent alveolar haemorrhaging in sub-chronic inhalation study with exposure groups 0, 10, 30, 100 and 300 µg/m3 (rats, 6 h/d, 10 d):
* effect ceased after exposure was stopped and developed rapidly on reintroduction of exposure up to 12 wk post-exposure
* Negative mutagenicity *in vitro* in bacteria, non-clastogenic *in vitro* in CHO cells.

Insufficient data to recommend a carcinogenicity notation. |
| DFG 1981 MAK: 0.04 mg/m3 |
| Summary of additional information:Air concentrations of 0.14–0.27 mg/m3 associated with local irritation, breathing impairment and immunological responses in exposed workers. Contact of substance with hot surfaces produces fumes, which cause irritation and lung damage. In rats, effects observed at acute exposures of 0.17 mg/m3 or 0.1 mg/m3 after 1 wk. Based on weight of evidence, provisional MAK of 0.04 mg/m3 considered protective of local irritation.Classified as a respiratory sensitiser, acute high exposures should be avoided, peak limitation factor of 1 therefore recommended. Provisional MAK not considered protective of this effect.Human data:* Air concentrations of 1.5–7.5 and 0.14–0.27 mg/m3 associated with adverse effects in 2 workplace studies:
	+ lower incidence of adverse effects reported at 0.14–0.27 mg/m3 following 2 yr of improved workplace conditions (no further details provided)
* Irritation of mucous membranes, cough, breathing impairment and evidence for immunological responses in exposed workers (n=6, no further details provided)
* Severe pulmonary impairment, haematopoietic disturbances, cough and lung infiltration reported in separate workplace study (no exposure details provided):
* effects resolved at 3 wk and 1 yr follow-up.

Animal data:* Focal haemorrhaging in lung tissue at 0.17 mg/m3 in repeat inhalation study with dose groups 0.17, 0.38 and 3.4 mg/m3 (rats, 6 h/d, 5 d/wk, 2 wk):
	+ extrapolated NAEC: 0.065 mg/m3
* Focal haemorrhaging in lung tissue at 0.1 mg/m3of smoke in repeat inhalation study (rats, 6 h/d, 5 d/wk, 2 wk); no lung changes observed after 1 wk.

Insufficient data to recommend notations for carcinogenicity or skin absorption. |
| SCOEL NA NA |
| No report. |
| OARS/AIHA NA NA |
| No report. |
| HCOTN 2010 not established |
| Summary of additional information:No existing administrative OEL available. Induction of allergenic effects considered the critical effect of exposure. HBROEL not derived due to lack of accepted level of additional sensitisation risk in the Netherlands. Additional risk estimates based on cohort study of exposed workers (n=286, also reported by ACGIH, 2018):* 10% incidence of substance-specific sensitisation estimated from fitted dose-response curve at 18 µg/m3
* 18 µg/m3 used as point of departure for linear extrapolation to 1 and 0.1% predicted sensitisation incidence risk:
	+ 1.8 µg/m3 (1% increased risk); 0.18 µg/m3 (0.1% increased risk).
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### Secondary source reports relied upon

| Source |  | Year | Additional information |
| --- | --- | --- | --- |
| NICNAS |  | 2014 | * Critical effect is respiratory sensitisation; exposure may also cause eye and respiratory tract irritation and skin sensitisation
* Presence of a solvent increases the dermal sensitisation potential in studies with rodents:
	+ under conditions of normal manufacture and use, substance unlikely to be used in a solvent and should be considered a potential dermal sensitiser
* Dermal LD50 >2,000 mg/kg (rabbits), 5,600 mg/kg (rats)
* Consistently negative mutagenicity results *in vitro* with bacteria and Chinese hamster ovary cells.
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| ECHA |  | 2020 | * High hazard; no long-term or short-term DNELs recommended.
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| OECD |  | 2002 | * Grouped assessment with trimellitic acid
* Elevated antibody levels and lung foci at 0.002–0.054 mg/m3 in sub-chronic inhalation study (rats, 13 wk, no further details on exposure provided); NOAEC not determined in this study
* Non-mutagenic in 3 *in vitro* studies with bacteria and mammalian cells; no *in vivo* data were available.
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### 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 | Respiratory sensitisation – category 1, Skin sensitisation – category 1 |
| NICNAS | Respiratory sensitisation – category 1, Skin sensitisation – category 1 |
| EU Annex | Respiratory sensitisation – category 1, Skin sensitisation – category 1 |
| ECHA | Skin Sens. 1 |
| ACGIH | Skin, DSEN, RSEN |
| DFG | Sa (respiratory sensitiser) |
| SCOEL | NA |
| HCOTN | Respiratory sensitiser |
| IARC | NA |
| 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  |
| --- |
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|  |  |  |  |
| --- | --- | --- | --- |
| Adverse effects in human case study: | yes | 4.00 |   |
| Dermal LD50 ≤1000 mg/kg: | no |   |   |
| 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** |

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### IDLH

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

## Additional information

| Molecular weight: | 192.12 |
| --- | --- |
| Conversion factors at 25°C and 101.3 kPa:  | 1 ppm = 7.86 mg/m3; 1 mg/m3 = 0.13 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) (2000) Trimellitsäureanhydrid (Rauch) – MAK value documentation.

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European Chemicals Agency (ECHA) (2019) Benzene-1,2,4-tricarboxylic acid 1,2-anhydride – REACH assessment.

Health Council of the Netherlands (HCOTN) (2010) Cyclic acid anhydrides. Health-based recommended occupational exposure limit. The Hague: Health Council of the Netherlands; publication no. 2010/02OSH.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2014) 5-Isobenzofurancarboxylic acid, 1,3-dihydro-1,3-dioxo-: Human health tier II assessment – IMAP report.

Organisation for Economic Cooperation and Development (OECD) (2002) SIDS initial assessment profile – Trimellitic Anhydride (TMA) Trimellitic Acid (TMLA).

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).