TITANIUM DIOXIDE

CAS number: 13463-67-7

Synonyms: Anatase, brookite, rutile

Chemical formula: TiO_2

Workplace exposure standard (amended)

TWA: **1 mg/m^3 (inhalable fraction)**

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 1 mg/m^3 (inhalable fraction) is recommended to protect for reduced lung function and potential cancer associated with overloaded pulmonary clearance in exposed workers.

Discussion and conclusions

Titanium dioxide (TiO_2) is used as a pigment, additive in the production of polymers, electronics and pharmaceuticals and food colourant. The two most commonly used forms in industry are derived from the rutile or anatase mineral.

The critical effect of exposure is reduced pulmonary function associated with inert particle overload in the lungs. Consequent carcinogenicity is reported in chronically exposed rats.

From the available epidemiological data, it is not certain that occupational exposure causes increased carcinogenicity (ACGIH, 2018; DFG, 2019; IARC, 2010). Carcinogenicity induced by chronic inflammation from lung overload is reported in rats exposed by inhalation or intratracheal instillation (ACGIH, 2018; IARC, 2010). Under these conditions, rats are considered more susceptible to carcinogenicity than other species and humans (ECHA, 2020). Depending on the particle size, a NOAEC for lung overload ranges between 0.5 and 10 mg/m^3 in sub-chronic and chronic inhalation studies in rodents (ACGIH, 2018; DFG, 2012).

The available exposure data in animal models suggest protection for inspirable particle overload in the lungs and that the resultant chronic inflammation is protective of carcinogenicity (ACGIH, 2018; DFG, 2012, 2019). DFG (2012) modelled an equivalent NAEC of approximately 1 mg/m^3 for humans based on the dose-response data for chronic inflammation and bioaccumulation in the lungs reported in several sub-chronic inhalation studies with rodents. This value of 1 mg/m^3 was adopted as the recommended MAK in 2019. The current SWA TWA of 10 mg/m^3 is potentially unprotective of bioaccumulation and chronic inflammation based on the lowest NOAEC of 0.5 mg/m^3 in rats. A TWA

of 1 mg/m^3 by DFG (2019) is recommended and expected to be protective of the effects of chronic lung overload.

Recommendation for notations

Not classified as a carcinogen according to the Globally Harmonized System of Classification and Labelling of Chemicals (GHS). However, there is some evidence for carcinogenicity due to chronic lung inflammation in animals. Based on this evidence, DFG (2019) classifies the substance as a Category 4 carcinogen, which is equivalent to a Category 1 or 2 carcinogen according to the GHS. ACGIH (2018) does not consider this evidence relevant to carcinogenicity in humans. Therefore, a review of the carcinogenicity classification is recommended.

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

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

APPENDIX

Primary sources with reports

Source	Year set	Standard
SWA	***1991***	***TWA: 10 mg/m^3***
ACGIH	***2001***	***TLV-TWA: 10 mg/m^3***

TLV-TWA intended to protect for potential respiratory tract irritation and pulmonary overload.

Not classifiable as a human carcinogen based on negative or inconclusive results of chronic animal inhalation studies.

Summary of information:

TLV-TWA recommendation based on chronic NOAEC of 10 mg/m^3 for lung overload in chronic inhalation study with rats, supported by epidemiological data that indicate no association between occupational exposure and chronic respiratory disease.

Human data:

- Non-toxic by ingestion; reported ingestion of 0.453 kg did not cause harm and eliminated in faeces within 24 h
- Inconclusive evidence for carcinogenicity in several case reports of chronically exposed workers:
  - not considered in agency's evaluation due to confounding smoking habits and insufficient exposure details
- No significant association between occupational exposure and respiratory disease, including cancer, reported in cohort study of production workers from 1935–1984 (n=1,576, employed for at least 1 yr).

Animal data:

- Substance is inert, not absorbed and has no toxic effect
- Dark deposits in pulmonary parenchyma and traces of alveolar macrophage infiltration in 1 case, incipient diffuse fibrosis in another at 50 mg in sub-chronic intratracheal instillation study (rats, no further details provided)
- Diminished ventilation within 1 wk in repeat intratracheal instillation study (rabbits, no further experimental details provided):
  - effects reversible within 3 mo
- Focal emphysema associated with dust aggregates at 10–328 mppcf (million particles per cubic foot) ≈33–1,093 mg/m^3 (rats, 2 h/d, 5 d/wk, 13 mo)
- No increased incidence of tumours compared to controls at 2.5 and 5% of diet in chronic feeding study (rats, mice, 2 yr)
- NOAEC of 10 mg/m^3 for lung overload manifested as accumulation of macrophages, foamy dust cells and free particles in chronic inhalation study with dose groups 0, 10, 50 and 250 mg/m^3 (rats, 6 h/d, 5 d/wk, 2 yr):
  - pulmonary overload at 50 mg/m^3
  - squamous cell carcinoma at 250 mg/m^3 after 2 yr, authors of cited article conclude that the type of tumour was caused by pulmonary saturation and of questionable relevance to occupational exposure.

Insufficient data to recommend a TLV-STEL or notations for skin absorption or sensitisation.

Source	Year set	Standard
DFG	***2018***	***MAK: 0.3 mg/m³ × material density (inhalable fraction)***

Summary of additional information:

Previous carcinogenicity classification of 3A withdrawn and category 4 notation recommended because threshold for inflammatory carcinogenic mechanism of action has been established.

Skin notation not warranted due to lack of evidence for dermal absorption.

No evidence for sensitising potential in humans or animals.

MAK derived from general recommendation for granular biopersistent dust. From *MAK documentation for granular biopersistent dust* (DFG, 2012):

Model calculations accounted for lung clearance mechanisms and orinasal inhalation in humans compared to nasal inhalation in rodents. These calculations used the dose-response relationships interpreted from several sub-chronic inhalation studies with rodents exposed to granular biopersistent dusts (GBD) including TiO_2 and determined a human equivalent concentration (HEC) of a NOAEC ≈0.5 mg/m³. It was difficult to select a NOAEC depending on the dose groups and substances tested in some of these studies. The resultant HEC from 3 separate model calculations of different GBD are 0.11, 0.25 and 0.5 mg/m³ assuming a specific density of 1 g/cm³. The average of these calculated values is 0.3 mg/m³ and is recommended as the general MAK for GBD, which should be multiplied by the specific density of the dust material. For TiO_2, a MAK of 1 mg/m³ is recommended based on the specific density of 3.9–4.3 g/cm³.

Human data:

- No clinical evidence for contact dermatitis or respiratory sensitisation:
  - 0.1% formulations in petrolatum used to test allergic response to Ti with isolated positive dermal sensitisation;
  - agency questions reliability of these data in view of the extremely low solubility of the substance
- Increase in blood pressure and decrease in pulmonary function in case study of production workers (average age: 36.57, average employment duration 8.64 yr, no details on exposure concentrations)
- No overall positive association between occupational exposure and cancer deaths and non-malignant respiratory or heart disease based on SMR in epidemiological study of production workers at 3 facilities (n=5,054, average age: 31).

Animal data:

- Transient white foci and alveolar emphysema at 25 mg/m³ TiO_2 nanoparticles or 45 mg/m³ fine particles (comparable surface areas) in repeat inhalation study (rats, 6 h/d, 21 d)
- Negative sensitisation in local lymph node assay (LLNA) with 2.5–10% formulations in olive oil/acetone
- Agency concludes substance is non-mutagenic *in vitro* based on overall negative results of several genotoxicity assays.

From *MAK documentation for granular biopersistent dust* (DFG, 2012):

- Several sub-chronic inhalation studies with TiO_2 consistently showed increased inflammatory responses, changes to lung epithelia and accumulation in the alveoli and terminal bronchioles up to 1 yr after exposure cessation:
  - increased leukocyte counts and changes in lung epithelium at 10–250 mg/m³ of fine TiO_2 or 2–10 mg/m³ of ultrafine TiO_2; epithelial hypertrophy and hyperplasia at 250 mg/m³ observed at 1-yr follow-up (mice, rats, hamsters, 6 h/d, 5 d/wk, 13 wk); NOAEC of 10 mg/m³ of fine TiO_2 and 0.5 mg/m³ of ultrafine TiO_2

Source	Year set	Standard
	○	no NOAEC based on lung clearance levels recorded at exposure cessation determined in separate sub-chronic study with exposure groups0, 0.5, 2 and 10 mg/m^3 ultrafine TiO_2 (rats, mice, hamsters, 6 h/d, 5 d/wk, 13 wk) ▪ based on evidence for increased proliferation in terminal bronchioles and alveoli observed during 1-yr follow-up, NOAEC of 0.5 mg/m^3.
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
NICNAS	✓	2016	• Substance does not penetrate skin, no dermal toxicity expected • LC_{50}: >3,430 mg/m^3 (rats, 4 h); no signs of toxicity, mottled and pale lungs observed at necropsy • Not expected to be irritating to eyes and skin (rabbits) • May potentiate respiratory sensitivity to allergens, but available data insufficient to warrant classification • Non-sensitising to skin based on negative results of 2 OECD-compliant sensitisation tests (guinea pigs) and LLNA test (also cited by DFG, 2019): ○ consistent with lack of reports of dermal sensitisation in humans exposed through topical sunscreen • Weight of evidence from *in vitro* and *in vivo* genotoxicity assays suggests substance is non-genotoxic.
IARC	✓	2010	• Weak evidence for increased risk of cancer in humans suggested by limited epidemiological data: ○ agency considers this evidence inadequate for classification • Increased lung tumour incidence in rats, only when exposed by chronic inhalation or intratracheal instillation: ○ considered sufficient evidence for carcinogenicity in animals • Overall evaluation: possibly carcinogenic to humans (2B).

Source		Year	Additional information
ECHA	✓	2020	• Rats are more susceptible than other model species and humans to formation of lung tumours caused by particle overload from insoluble low-toxicity particles: ○ particle overload observed in chronically exposed mice, but without fibroproliferative disease as reported in chronically exposed rats ○ lower susceptibility of humans substantiated by lack of evidence for increased tumorigenicity in epidemiological data.
OECD	✓	2013	• Majority of mutagenicity assays *in vitro* suggest substance is non-mutagenic • Negative in sex-linked recessive lethal assay with *Drosophila melanogaster* and 2 other non-guideline *in vivo* mutagenicity assays (mice, rats).
US NIOSH	✓	1994	• IDLH: 5,000 mg/m^3 based on being 500 times the OSHA PEL of 10 mg/m^3 promulgated in 1989 (respiratory protection factors).

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	NA
NICNAS	—
EU Annex	NA
ECHA	—
ACGIH	Carcinogenicity – A4
DFG	Carcinogenicity – 4
SCOEL	NA
HCOTN	NA
IARC	Carcinogenicity – Group 2B
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	
Adverse effects in human case study:	no
Dermal LD_{50} ≤1000 mg/kg:	
Dermal repeat-dose NOAEL ≤200 mg/kg:	
Dermal LD_{50}/Inhalation LD_{50} <10:	
In vivo dermal absorption rate >10%:	no
Estimated dermal exposure at WES >10%:	no
	a skin notation is not warranted

IDLH

Is there a suitable IDLH value available?	No

Additional information

Molecular weight:	79.86
Conversion factors at 25°C and 101.3 kPa:	1 ppm = 3.27 mg/m^3; 1 mg/m^3 = 0.31 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* on the ACGIH website.

Deutsche Forschungsgemeinschaft (DFG) (2018) Titandioxid (alveolengängige Fraktion) – MAK value documentation, German language edition.

Deutsche Forschungsgemeinschaft (DFG) (2012) Allgemeiner Staubgrenzwert (A-Fraktion) (Granuläre biobeständige Stäube (GBS)) – MAK value documentation, German language edition.

European Chemicals Agency (ECHA) (2020) Titanium dioxide – REACH assessment.

International Agency for Research on Cancer (IARC) (2010), Volume 93, Carbon Black, Titanium Dioxide and Talc. IARC Monographs on the evaluation of the carcinogenic risk to humans.

National Industrial Chemicals Notification and Assessment Scheme (NICNAS) (2016) Titanium dioxide: Human health tier II assessment – IMAP report.

Organisation for Economic Cooperation and Development (OECD) (2002) SIDS initial assessment profile – Titanium dioxide.

US National Institute for Occupational Safety and Health (NIOSH) (1994) Immediately dangerous to life or health concentrations – Titanium dioxide.