

TDMA/TDIC SCIENTIFIC POSITION REGARDING THE FRENCH PROPOSAL FOR A HARMONISED CLASSIFICATION OF TITANIUM DIOXIDE

Summary

- In May 2016, the French competent authority (ANSES) submitted a harmonised classification proposal to the European Chemicals Agency (ECHA) for titanium dioxide (TiO₂) as a category 1B (presumed to have carcinogenic potential for humans) by inhalation.
- The Titanium Dioxide Manufacturers Association (TDMA) and the Titanium Dioxide Industry Consortium (TDIC) consider the French competent authority proposal to be scientifically unjustified and argue that TiO₂ should not be classified.
- The ANSES proposal is based on the results of inhalation studies conducted more than 20 years ago in which rats were exposed to levels of TiO₂ dust well above OECD guideline testing levels and many times the levels ever encountered during manufacture and use. Use of this data risks the validity of standardised chemical classification.
- It has been conclusively shown that the response to these lung overload studies with poorly soluble particles is unique to the rat and is not seen in other animal species or humans.
- Detailed studies of over 24,000 workers in 18 manufacturing sites over several decades has confirmed no adverse respiratory or other health effects from exposure to TiO₂.

SCIENTIFIC CONSIDERATIONS

1. Results from rat studies under overload conditions are not applicable to humans

The classification proposal in the French harmonised classification and labelling (CLH) report is based on a small number of studies in rats exposed to extremely high concentrations (i.e. 250 mg/m³) of titanium dioxide dust leading to “lung overload” effects and tumours. The observed effects are a secondary result of particle-induced inflammatory processes in the lungs due to **dust inhalation alone and not to the specific nature of titanium dioxide**. This effect is found exclusively in the rat and is not specific to titanium dioxide; tests on mice and hamsters do not show carcinogenicity.

Tests at more realistic dose levels do not result in carcinogenicity in any species tested and all but one of the rat tumours originally identified as carcinogenic have been reclassified as benign on more recent review¹.

The studies used in the French report have been known for over 20 years and there is no new scientific information that has been introduced by the French CLH report supporting the need for titanium dioxide classification.

Moreover, all relevant guidance documents, published by ECHA², OECD³ and the ECETOC Report⁴, observe that the results from “lung overload” studies in rats should not be transferred to humans.

Therefore, we believe that the classification as proposed by France is not scientifically justified from a toxicological perspective.

TDMA and TDIC also believe that the acceptance of effects seen at dose levels well above standard OECD guideline levels or maximum tolerated dose levels for relevant species would compromise the validity of standardised chemical classification.

2. No indications of human carcinogenicity hazard from extensive epidemiological studies or extensive practical use in diverse applications

Titanium dioxide has been safely used for many decades in a massive range of products and applications with no evidence of carcinogenic or other adverse human health effects.

Epidemiological studies covering more than 24,000 production workers at 18 TiO₂ manufacturing sites over several decades found no increased incidence of lung cancer as a result of workplace exposure to TiO₂⁵. The French CLH report dismisses the value of these worker health studies and has omitted the inclusion of the most recent study that was provided in the REACH titanium dioxide registration dossier.

The French classification proposal relies on rat studies which exposed the animals to dust levels of up to 250mg/m³ which are far higher than those to which workers are allowed to be exposed during a normal working day (10mg/m³).

3. A classification as a carcinogen in any Category is not justified

We have reviewed the responses to the French CLH report public consultation from July, and noted that the majority of the submissions, including those from esteemed inhalation toxicology scientists, do not support classification of TiO₂.

Whilst there is clear evidence as described in Section 1 that effects seen in rats are not relevant to humans, some Member States' responses to the French CLH report propose that a Cat 2 carcinogen classification would be appropriate. We assume this is based on the proposals of the MAK Commission

¹ Warheit DB, Frame SR. Characterization and reclassification of titanium dioxide-related pulmonary lesions. *J Occup Environ Med*. 2006 Dec; 48(12):1308-13

² ECHA guidance on the Application of the CLP Criteria (Version 4.1, June 2015), (section 3.6.2.3.2., p.379-380)

³ OECD (2012) Guideline document 116 on the conduct and design of chronic toxicity studies

⁴ ECETOC Report: Technical Report No. 122: Poorly Soluble Particles / Lung Overload. <http://www.ecetoc.org/publication/tr-122-poorly-soluble-particles-lung-overload/>

⁵ TDMA/TDIC comments and response on CLH proposals on Titanium Dioxide (comment n. 99, references Boffetta, P et al, Ellis, E.D et al, Fryzek, J.P et al).

on Granular Bio-persistent Particles⁶. However, Morfeld⁷ et al have identified significant flaws in the assumptions used in the modelling behind the MAK work. Furthermore, recent modelling by Oberdörster⁸ has conclusively demonstrated the differences in lung responses between rats, other rodents and humans. Whilst at a superficial level this could be seen as a precautionary response the science does not support this conclusion.

Other respondents to the public consultation suggested that there is a difference in the carcinogenic potential of nano and pigmentary TiO₂. However, the scientific evidence together with the modelling work by Oberdörster does not support this conclusion.

Conclusion

TDMA and TDIC believe that the French proposal for classification and labelling of titanium dioxide is unjustified from a toxicological perspective for the following reasons:

- The observed effects are based on old studies carried out at extremely high concentrations (250mg/m³), well above OECD guideline levels. No carcinogenicity was seen at normal test levels.
- Tumours were observed only in rats and under overload conditions, the results are not applicable to humans
- All but one of the observed tumours in rats was reclassified as benign on more recent review.
- There is extensive epidemiology data showing no adverse health effects on TiO₂ workers

Therefore, a balanced analysis of the science does not support classification.

For the above reasons, TDMA and TDIC believe that the current “no” classification status for titanium dioxide is correct and must be retained.

For more detailed information on the scientific justification for “no classification”, please refer to [TDMA/TDIC comments and response on CLH proposals on Titanium Dioxide](#) (comment n. 99, p. 77-85).

⁶ German MAK Commission. Technical report 122, December 2013. ISSN-0773-8072-122

⁷ Morfeld P et al, Morfeld P, Bruch J, Levy L, Ngiewih Y, Chaudhuri I, Muranko HJ, Myerson R, McCunney R. Translational toxicology in setting occupational exposure limits for dusts and hazard classification – a critical evaluation of a recent approach to translate dust overload findings from rats to humans. *Particle and Fibre Toxicology*. 2015; 12:3. doi:10.1186/s12989-015-0079-3

⁸ G Oberdörster, Annex to CLH report, CLH Report Comments 7 15 16

About Titanium Dioxide

Titanium is the 9th most abundant element in the world and Titanium Dioxide (TiO₂) is the oxide of the metal, which occurs naturally in several kinds of rock and mineral sands.

Pure TiO₂ is a fine, white powder and is the brightest, whitest pigment available. Highly refractive, ultraviolet absorbing, non-toxic and inert, TiO₂ has been used for many years (nearly 100) in a vast range of industrial applications and consumer goods to impart whiteness and opacity to paints, printing inks, plastics, textiles, ceramics, construction materials, cosmetics, food, pharmaceuticals, etc.

Although best known for its whiteness, nearly all coloured paints also require the addition of TiO₂ for opacity and brightness and plastics require TiO₂ to prevent degradation by UV light. The reality is that in the world we live in we are surrounded by TiO₂ and have been for many years.

TiO₂ is produced primarily in the pigmentary form (over 98% of total production) making use of its excellent light-scattering and UV absorption properties in the wide range of applications listed above. TiO₂ is also produced as an ultrafine (nanomaterial) product where different properties are utilised. For example the smaller particle size gives a transparent UV light absorber that is required in cosmetic sunscreens or gives the high surface area required in catalyst support applications for the treatment of harmful emissions in the automotive industry and for the removal of oxides of nitrogen (NO_x) from power station emissions.

Learn more about the uses of titanium dioxide at <http://brilliantwhite.life/>

About TDMA

The Titanium Dioxide Manufacturers Association - TDMA is a sector group of Cefic (the European Chemical Industry Council) and it represents the major producers of Titanium Dioxide (TiO₂) and acts as their responsible voice in Europe since 1974.

TDMA promotes and defends the merits of Titanium Dioxide (TiO₂) in all suitable applications by bringing forward evidence of its safety and efficacy.

TDMA is a non-profit organisation and it has no commercial role. For all commercial enquiries, please refer to the websites of our members.

About TDIC

The manufacturers of Titanium Dioxide have joined efforts for their REACH compliance activities and have launched the TDIC REACH consortium.

The Titanium Dioxide Industry Consortium (TDIC) manages the REACH registration of titanium dioxide and related manufacturing process intermediates, and liaises with registrants of key raw materials in other consortia and SIEFs.

For further information, please contact the TDMA Secretariat, at tdma@cefic.be.