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PERSPECTIVE

Weight of epidemiological evidence for titanium dioxide risk assessment: current state and further needs

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Abstract

We address here the importance of epidemiological evidence in risk assessment and decision-making in Europe. To illustrate this, titanium dioxide (TiO_2) was used as a model compound. TiO_2 is widely used as an odorless white pigment and opacifying agent. A recent systematic review assessing the weight of evidence on the relationship between exposure to TiO_2 (all forms) and cancer in humans questions the assumptions that TiO_2 is an inert material of low toxicity. Based on this new data, France submitted a proposal to classify TiO_2 as a possible human carcinogen under the European regulation. The European Chemicals Agency Risk assessment committee concluded that TiO_2 (all forms) warrants a classification as a suspected human carcinogen via inhalation (Category-2) under the CLP regulation (for Classification, Labeling and Packaging of chemicals). No considerations was given to TiO_2 particle size, which may affect human health effects. Consequently, further epidemiological studies are needed to assess possible associations between different physical–chemical characteristics of TiO_2 exposures and their impact on human health. This would allow strengthening the evidence on which to build the most appropriate regulation and to guaranty safe use given any exposure route of any TiO_2 particle shape or size.

Keywords Lung cancer · Nanoparticle · Systematic review · Occupational exposure · Bias · Policy

Introduction

In a recent article, Deener et al. [1] advocated that epidemiology can strengthen risk assessments, and highlighted several examples from the US-EPA. The authors also listed factors that can facilitate the appropriate use of epidemiologic studies in environmental decision-making. In particular, they recommend incorporating conclusions on causal inferences drawn from evidence by using systematic review methods and accounting for study quality when weighing the evidence. Here, we explore the applicability of this strategy in Europe, and we use titanium dioxide (TiO_2) as a model.

TiO_2: the rationale for the risk assessment in the European framework

TiO_2 is a white, odorless pigment and an opacifying agent, manufactured from mineral ores or from iron titanate or titanium slag and became commercially available in 1920. TiO_2 is widely used in industrial and professional settings, and included in numerous products and articles such as paints, varnishes, inks, coatings, plastics, rubbers, papers, plasters, adhesives, coated fabrics and textiles, glassware, ceramics, electroceramics, electronic components, catalysts, welding fluxes, welding rods, floor coverings, roofing granules, food additives (E 171), pharmaceuticals, cosmetics, dental impressions, water and surfaces treatment.

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The vast use is due to TiO_2 numerous properties e.g., thermal stability, resistance to chemical attack, resistance to ultraviolet (UV) degradation (UV blocker), and photocatalysis potential. Since the 2000's its annual world-wide production is about 5 million metric tons and remains constant [2]. TiO_2 is produced in different particle size fractions. When the particle size is in the nanoscale (i.e., <100 nm or 100 x 10^{-9} m) in one or more dimensions, TiO_2 exhibits enhanced photocatalytic and resistance properties. Since 1990, TiO_2 has been specifically engineered as nanoparticles, nanosheets, and nanotubes [3].

For decades, TiO_2 was considered a poorly soluble inert material of low toxicity [4]. In 2006, the International Agency for Research on Cancer (IARC) classified TiO_2 as potentially carcinogenic to humans (group 2B) [5]. This classification did not affect the European regulation. France, however, initiated a classification process under the European Regulation (EC) No 1272/2008 to change the European legislation based on the sufficient evidence of carcinogenic properties of TiO_2 in experimental animals identified by the IARC, and the rising concerns from nanoparticle toxicity studies in general [6]. This initiative was submitted under the CLP regulation (for **C**lassification, Labeling, and Packaging of chemicals) [7], which is the only legislation in force for classification and labeling of substances and mixtures in Europe. The CLP regulation states that once a substance or mixture is classified, the identified hazards must be communicated to other actors in the supply chain, including consumers (via label and safety data sheet). The purpose is to alert stakeholders about the presence of a hazard and the need to manage the associated risks. The substance and mixture classification affect other EU legislations such as Worker Directive (CMD 2004/37/EC), which sets binding occupational exposure limit values, as well as biological limit values.

France submitted a classification proposal for all existing forms of TiO_2 as carcinogen category 1B ("presumed human carcinogen") by inhalation to the European Chemical Agency (ECHA). ECHA manages the technical and administrative aspects of the implementation of REACH (Registration, Evaluation, Authorization and Restriction of Chemicals Regulation) regulation No 1907/2006. The registered dossier included data available from the industry and scientific literature. The classification proposal was based on sufficient evidence of carcinogenicity in animals and inadequate evidence in humans. During the public comments in 2016, several stakeholders questioned the epidemiological conclusions in the classification proposal, concluding that epidemiological data were actually adequate, and that they do not report any increased risk of respiratory cancer after occupational exposure to TiO_2. In the light of these controversial views, the epidemiological data were re-assessed by France especially focusing on the relevance of carcinogenic effects observed in rats that were extrapolated to humans as stipulated under the CLP framework.

Weight of evidence for TiO_2 carcinogenicity in human

We conducted a systematic literature review of epidemiological data, including all forms of TiO_2. The bibliographical corpus on which IARC based its conclusions [2] was regarded as an initial corpus. We supplemented the corpus adding a search for documents published afterwards and up to 31st of August 2015. The query was composed of combinations of keywords—including Titanium Dioxide, TiO_2, Human study/ies, Epidemiological study/ies, Cohort study/ies, Case–control study/ies—using OR and AND operators. Two databases (SCOPUS and PubMed) were queried, and the title, abstract and keywords sections were searched. The weight of evidence of TiO_2 carcinogenicity in humans was documented and assessed according to the guidelines prescribed by the "Risk Assessment Methodology" by the work group of ANSES, the French Agency for Food, Environmental and Occupational Health & Safety [8]. Each article identified and not excluded was reviewed separately by two independent experts, using a standardized evaluation form [8]. This form specified critical aspects of the study under consideration such as the design (type of study, population, exposure, output, timing, settings), the statistical analysis (statistical models, adjustment, etc.), and the results (strength or weakness of the association and bias). The study funding and potential for conflicts of interest were also reported. An analysis of the risk for bias according to the approach proposed by the OHAT [9] completed this evaluation.

Two additional cohort studies [10, 11] were identified along with historical cohorts of workers [12–14] considered by IARC [2]. Two identified case–control studies considered by IARC [15, 16] conducted in the general population included a broad array of workers not specifically exposed to TiO_2. Consequently, we excluded these two case–control studies from our targeted TiO_2 review. Two experts reviewed these cohorts (Supplementary information, Fig. S1 and Table S1). Statistically significant increase of mortality for lung cancer was reported in two independent populations (one US and one European) among the included cohort studies [11, 12]. All studies suffered from selection and exposure misclassification bias, along with confounding effect of smoking and occupational exposures other than TiO_2. In particular, there were weakness and inconsistencies in exposure assessment in all studies available. The major and commonly shared drawbacks were the use of area air concentrations instead of individual

measurements of TiO_2 concentration. Personal sampling data were rarely available. We noted several inconsistencies in sampling and statistical methods. The TiO_2 exposure was either assessed as an aerosol, i.e., use of measurement data based on inhalable fraction (comprising coarse, fine and ultrafine particles, such as total dust) or as a respirable fraction (comprising only fine and ultrafine particles). Statistical treatment of the measurement data reported inconsistent choices of exposure cutoffs. These inconsistencies in exposure assessments could affect the strength of the observed exposure-response effect by lowering the risk estimates toward the null while overestimating the exposure, and finding statistically non-significant estimates arising from high uncertainty and errors in exposure variables. The young age of the workers (around 30-years-old) at study entry and a follow-up duration that might be shorter than the latency-time needed between TiO_2 exposure and the occurrence of lung cancer were additional drawbacks. Nevertheless, the main issue in all studies reviewed was the presence of the healthy worker effect and in particular, the healthy worker survivor effect (HWSE) [17]. Some authors identified and discussed the HWSE [10, 14]. The HWSE is of primary concern in exposure-mortality analyses because it may hide or underestimate the association when the exposure of interest is highly correlated with duration of employment. Mortality rates in occupational cohorts tend to change between the period of active employment and the period following termination of employment [18]. This temporal variation in mortality rates has not been addressed in TiO_2 worker cohorts, however. Such an effect seems very likely to have masked or underestimated the association between TiO_2 exposure and mortality. Consequently, the HWSE along with all other limitations described above may explain the lack of association between cancers and exposure to TiO_2 as considered in previous evaluations.

Considering the methodological bias in combination with statistically increased mortality by lung cancer reported in two publications [11, 12], France established that the human data are not sufficient to conclude at the lack of carcinogenic effect in humans and cannot contradict the carcinogenic effects observed in rats [6].

Integration of epidemiological evidence in the European policy and decision-making

The ECHA Committee for Risk Assessment (RAC) comprises experts nominated by the Member States, but acting in their own capacity. The ECHA RAC's opinion delivered in September 2017 stated that the epidemiological studies cannot overrule the animal carcinogenicity studies [19]. The ECHA RAC concluded that a classification as a category-2 carcinogen (Suspected Human carcinogen) by inhalation should be included in Annex VI to the CLP regulation for TiO_2 under all forms. The final decision of the inclusion of a new classification in Annex VI to the CLP regulation is the responsibility of the European Commission. For the time being, the European Commission has not made a final decision regarding TiO_2.

If endorsed by the European Commission, the classification as Category-2 carcinogen by inhalation would preclude further consideration of TiO_2 as insoluble low-toxicity particles, not otherwise regulated or classified. In particular, all actors in the supply chain should be informed of the suspected carcinogenicity of TiO_2 with the implementation of specific risk mitigation measures. This classification could also prompt additional risk management measures for TiO_2 (e.g., exposure reduction and control, setting of exposure reference values, production of less toxic ("safe by design" forms)). These risk management measures would require more specific risk assessments for specific TiO_2 forms and thus, these knowledge gaps would need to be addressed.

Scientific advances to strengthen the epidemiological evidence in TiO_2 risk assessment

Our systematic review raised the need to characterize the HWSE and reassess the exposure-mortality association for lung cancer in a large TiO_2 occupational cohort with adequate control for this bias. An adjustment for the time-since-termination of employment was efficient in reducing the HWSE confounding bias [18]. The G-estimation methods are an alternative approach in cases where termination of employment is an intermediate variable associated with the cause of death under investigation [20].

Another alternative would be to set-up a joint international cohort study based on rigorous standards of data harmonization where the exposure assessment is emphasized [21] and the analysis the exposure-mortality association for lung cancer with respect to TiO_2 exposure is a nested case–control study. Such an approach has been successfully applied to nuclear workers [22]. The latter approach facilitates additional data collection on potential confounders and improves individual exposure assessments [23, 24]. Incorporating adequate physical–chemical characterization of TiO_2 will be needed to assess the potential effect due to different TiO_2 forms used.

The classification for TiO_2 as proposed by the ECHA RAC is applicable to all forms of TiO_2 because there was no clear difference of carcinogenicity among the forms tested within the existing dataset. Some particular forms of TiO_2 (e.g., nanoparticles, fibrous-like, coated, etc.), however, might result in a more potent carcinogenicity or induce

other specific lesions via a specific mode of action. Thus, the category-2 carcinogenicity classification should be considered as a minimal classification for these specific forms in the absence of adequate data. Some physical–chemical characteristics of TiO_2 such as particle size, crystallinity, shape and coating might have an impact on toxicological properties. Consequently, these TiO_2 characteristics should be integrated in the exposure assessment in future epidemiological studies of TiO_2 exposed populations.

The particle size is a key parameter to address in order to distinguish between exposure to micro-sized (bulk) and nano-sized TiO_2. Several experimental studies have demonstrated that the nano-sized fraction is more "reactive" (biologically active) than the micro-sized fraction; however, none of the articles reviewed was able to associate a hazard to specific particle size. Nanoparticles are less efficiently cleared compared to fine particles made of the same material [25]. The explanation for this phenomenon is not yet clear, as the mechanism of phagocytic clearance of nanoparticles is not yet fully understood. Additionally, the contribution of direct cytotoxic effects—resulting from the greater surface area and therefore higher reactivity of nanoparticles, has been suggested [26, 27].

Crystal structure also influences particle reactivity. TiO_2 anatase form produce greater inflammation responses and/or cytotoxicity in vitro than the rutile form [28, 29]. Recent studies have shown that more severe toxic effects may be induced with the rutile form compared to the anatase [30]. At this time, the available in vivo studies do not provide sufficient evidence to decide which crystallinity is the most toxic and to what extent.

Coating or chemical surface treatment of TiO_2 particles is used to enhance or maintain TiO_2 properties and, more recently, to make it safer. For example, appropriate coating can quench surface photocatalytic activity and reduce the likelihood of generation of reactive oxygen species. Since oxidative stress is involved in the mechanism of carcinogenicity of TiO_2, it could be expected that some coatings at an unknown level can modulate this response. In contrast, some coatings may themselves release toxic material. All commercially produced TiO_2 (micro or nano-sized) particles with the exception of some compositions of TiO_2 used as a food additive are coated with a variety of organic or inorganic materials [2]. These coatings can be hydrophilic, hydrophobic, or amphiphilic, rendering them reactive. These coated particulates could then induce a greater lung inflammatory response than the equivalent non-surface treated particulates.

Shapes of TiO_2 particles such as spheres, nanorods, needles, tubes, fibers-like, etc. have been identified in the literature. They can be divided in two main types: spherical and elongated shapes. In the absence of experimental data, it might be hypothesized that some of the elongated shapes could behave similar to fibers. Fibers and granular particles induced lung tumors with a similar mode of action consisting in a persistent inflammation due to an incomplete phagocytosis and a release of reactive oxygen and nitrogen species. Fibers can also translocate to the pleura and induce malignant mesothelioma. This mode of action is not reported with granular spherical particles. Thus, fibers are suspected to induce more severe carcinogenic effects compared to granular forms.

Adequate characterization of TiO_2 in epidemiological studies is critical in understanding how and to what the extent specific forms of TiO_2 would lead to more severe toxicity [31]. None of the epidemiological studies on TiO_2 addressed this issue, even though this should be possible to address in a retrospective cohort study [32]. Exposures should be reviewed with particular attention to manufacturing processes, chemical and physical conditions, and final destination of use, which usually determine the characteristics of each TiO_2 batch produced [33, 34]. The three more recent cohorts [11, 12, 14] of TiO_2 exposed workers could be updated with respect to the physical–chemical properties of TiO_2 and ideally, with respect to morbidity and mortality outcomes. In the framework of an international joint-study, the former could be reconstructed based on a harmonized method allowing more powerful and detailed statistical analyses. Identification of workers exposed to TiO_2 nanoforms in existent cohorts could be challenging given that the production of these started relatively recently (in the 1990s). In light of this, new prospective longitudinal panel studies of workers exposed to nano-TiO_2 seem more appropriate [35]. The implementation of a specific occupational exposure limit for TiO_2 nanoforms should facilitate the identification of these workers and their inclusion in specific health surveillance programs and prospective epidemiological studies [3]. At the moment, there is no harmonized exposure limit set at the European level for TiO_2, neither for workers, nor for general population. A growing application of TiO_2 nanoforms led several countries to propose exposure limit values for nano-TiO_2. In France, the National Institute of Research and Security (INRS) issued a proposal [3] to follow the National Institute for Occupational Safety and Health (NIOSH) recommended occupational exposure limit of 0.3 mg/m^3 for the ultrafine fraction of a TiO_2 aerosol with a cancer risk of 1/1000 [3]. For the general population, a chronic toxicological reference value for TiO_2 nanoforms by inhalation of 0.12 $\mu g/m^3$ based on lung inflammation was recently proposed by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) [36]. However, this value is only applicable to TiO_2-P25 (80% anatase/20% rutile; 21 nm), which was the only TiO_2 form tested in the study used to establish this value [37]. Considering the large variety of

TiO_2 forms on the European market (>350) and in the absence of adequate toxicological data for these, this value might not apply to other forms of TiO_2 nanoparticles (different size, crystallinity, surface coating…).

Conclusion

The new epidemiological evidence questions the assumptions that TiO_2 is an inert material of low toxicity. In the CLP framework, the ECHA RAC concluded that the evidence from epidemiological data is inadequate and thus could not overrule the outcome from the animal studies. This triggers the classification of TiO_2 as a Carcinogen of Category-2: Suspected Human carcinogen by inhalation. This conclusion on human data is in line with the last IARC assessment and illustrates the relevance of epidemiological evidence for risk assessment and decision-making in Europe. Further epidemiological data are needed where different physical–chemical characteristics of TiO_2 and their impact on human health is incorporated. Updated retrospective and new prospective epidemiological studies with well-characterized TiO_2 exposure data are necessary to strengthen the evidence on which to build the most appropriate regulation and to guaranty a safe use of any form of TiO_2.

Disclaimer

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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