Substance classification of titanium dioxide illustrates limitations of EU legislation

The harmonized classification of titanium dioxide as a suspected carcinogen has the potential to misinform consumers and promote aversive behaviour. The case exemplifies the limits of a hazard-based classification system that should not be used without exposure assessment in downstream, sector-specific legislation.

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Titanium dioxide (TiO_2; used as E171 in food and as CI 77891 in cosmetics) is classified as a suspected carcinogen through the inhalation route by the European Commission[1]. Bulk E171 will, for example, be delivered from producers labelled as a category 2 carcinogen to downstream industry, but any resulting food product will not require labelling because of the obvious difference in the route of exposure. For consumers, some products containing the pigment may no longer be available, while others such as cosmetics and food continue to be marketed as before. The case of TiO_2 raises interesting questions about hazard communication as well as the handling, commensurability and practicability of substance classification in EU legislation.

One substance, one classification

Classification and labelling relies solely on hazard information, which in terms of health hazards is usually derived from deleterious health effects seen in animal testing, while risk assessment is based on the product of hazard and exposure, that is, the dose and duration of actual contact to the agent at hand. In the case of TiO_2, information on the kind of exposure found its way into the classification by virtue of respirable particles.

The deviation from the principle of 'one substance, one classification' that underpins the European Union regulation Classification, Labelling and Packaging (CLP)[2] creates a scenario that is not yet fully explained to the consumer. Some products, if they remain available to the consumer at all, will be labelled for carcinogenicity and/or include a bewildering array of notes and EU hazard statements while food and cosmetics state TiO_2 simply as an ingredient. In addition, the underlying data for the classification of TiO_2 as a carcinogen are based on high and chronic inhalation exposure, and point to a mechanism applicable to many dusts, particularly pigments. In our view, the potential to cause uncertainty for consumers about how to respond to the labelling of TiO_2, and in consequence, to the labelling system as a whole (and aversion towards products containing TiO_2), by far does not match the potential risk of carcinogenicity, occurring after chronic inhalation exposure to high doses.

From a regulatory perspective, widespread use of a substance — such as TiO_2 — is a common trigger for harmonized classification and labelling. The CLP regulation[2] is the implementation of the United Nations Globally Harmonized System for the European market. The aim of this regulation is to provide a high level of protection of human health and the environment while at the same time ensuring free trade of substances, mixtures and articles. It does so by providing a classification of the respective intrinsic substance hazards, the idea of which is to raise awareness, be readily accessible in case of emergencies, and be a basis for subsequent exposure-based assessments for substance handling and use. Within this concept, manufacturers, importers or downstream users of substances or mixtures are responsible for the appropriate classification, labelling and packaging of hazardous chemicals with classification being exclusively based on the hazardous properties as described in available reports. The regulation does not ask for performing any testing, and a classification should be adapted when new data becomes available. In addition, EU member states can propose so-called harmonized classification and labelling of a substance, primarily for the endpoints of carcinogenicity, mutagenicity, reproductive toxicity and respiratory sensitization. For substances that are not active substances in biocidal or plant protection products such a proposal can also be made by manufacturers, importers or downstream users. Harmonized classification and the resulting labelling are mandatory for all stakeholders.

The original intention of this process was to identify and prioritize substances for which subsequent exposure-based risk assessments are potentially needed in order to establish safe handling and use. As a result, harmonized classification requires labelling of all products and articles containing more than a certain concentration of a potentially harmful substance, depending on the classification. However, some EU regulations defy the original concept of performing subsequent risk assessments and instead automatically restrict or prohibit the use of substances with certain classifications as well as the processing of products containing the substance, including waste. The reasons for doing so are more political-administrative than scientific, with the intention of facilitating the implementation of protective measures against exposure to potentially hazardous substances. While originally well-intended, this 'shortcut' not only ignores the significance of exposure as a most critical factor for any substance to actually cause harm but also fails to acknowledge that it is not suitable for all substances. Moreover, if used in strict formality it will undermine the very purpose of a hazard-based classification as an essential but not exclusive building block for better public health protection. This problem is currently particularly well demonstrated for TiO_2 but applies equally to other substances.

Classify without exposure assessment

In the case of TiO_2, the French Competent Authority put forward a proposal for the harmonized classification and labelling of TiO_2 "in all phases and phase combinations and particles in all sizes/morphologies" as carcinogen category 1B ("presumed to have carcinogenic potential for humans; classification is largely based on animal evidence") for the inhalation route[3]. The

endpoints addressed in the proposal were germ cell mutagenicity and carcinogenicity, exclusively. Previously, TiO_2 had been classified as carcinogen category 1B by nine notifiers or as category 2 "suspected human carcinogen" by 115 notifiers according to the European Chemicals Agency (ECHA) classification and labelling inventory at the time of preparation of the proposal[3]. The reasons for the respective deviations in classification are mainly rooted in varying expert judgements regarding predictivity and transferability of particle testing by inhalation in rats. Subsequently, and following a public consultation, ECHA's committee for risk assessment (RAC) assigned a concluding classification as carcinogen category 2 for the inhalation route in September 2017[4]. Moreover, RAC suggested limiting labelling of TiO_2 to only the form of inhalable-sized particles. This is an exception to the Guidance on the Application of the CLP Criteria[5] which states: "The system of classification is designed to ensure that a single classification applies to a substance. In general, it takes no account of the specific form since this can vary and is not intrinsic to the substance." The classification, expanded by three notes and three EU specific hazard statements for mixtures, contributing to a confusing labelling, has been enacted in February 2020 and will come into force in September 2021. It had been held up in various EU committees due to differing concerns of member states. Leaving questions regarding the physico-chemical properties of the forms tested or the suitability of testing or conflicting epidemiological data aside, most concerns focused not so much on the classification but on the commensurability of the automatic legislative consequences in absence of any further toxicological risk assessment. This particularly concerns many products directly available to consumers, which are regulated in separate legislations, and in some cases specified by national law. Here we look at the impact of TiO_2 classification on the major product sectors.

Labelling by exposure route

TiO_2 is predominantly used as a white pigment with a very high refractive index. As such, it has been widely used for decades and is found in a vast assortment of consumer products such as inks, paints, paper, plastic articles, and toothpaste. It is also used as a food colouring agent, labelled E171, and is found in a wide range of processed foods. As a nanomaterial, it loses its white colour while retaining its capability of absorbing ultraviolet light, and is hence used in sunscreens and other products for UV protection[6].

Directly affected by the classification are containers of bulk E171 and potentially 'inhalable' products in hardware stores, such as cement, gypsum and dry paints, and some other applications such as line markers for playing fields and courts that contain TiO_2, all of which would have to be labelled as being potentially carcinogenic by inhalation. Since the classification pertains to inhalation exposure, no labelling would be required for textiles, cosmetics, or food. Note, however, that the recent opinion of the Scientific Committee on Consumer Safety on TiO_2 recommends a lower maximum concentration in aerosol spray cosmetic products[7].

While not related to this classification, it should be noted that the French government recently adopted a regulation that suspends placing foodstuffs containing E171 on the market for one year[8] on the basis of a study showing some effects on the immune system and changes in the intestinal mucosa after oral gavage[9]. Although it involves the immune system and hence macrophages, it should be noted that macrophages in the gut mediate tolerance to food and microbiota[10]. In contrast, in the lungs pro-inflammatory macrophages play a part in the above-mentioned aetiology of lung tumours. The European Food Safety Authority (EFSA) reviewed the study by Bettini et al.[9] and three other studies in 2018 and came to the conclusion that due to the studies' deficiencies, and taking into account the low oral bioavailability and exposure of TiO_2, the available data do not give rise to health concerns[11]. Likewise, TiO_2 is permitted in food contact materials made of plastics according to the regulation on plastic materials and articles intended to come into contact with food[12].

Altogether, the use of TiO_2 is therefore regarded as safe in cosmetics[7], textiles, food contact materials[12] and food[11]. Likewise, there have so far been no indications of a health risk for the use in toys. However, labelling of bulk TiO_2 including E171 and of products containing unbound TiO_2 in powder-form is mandatory. Many food additives require labelling in bulk, most frequently for acute toxicity, sensitization, and irritation. While in those cases it is understood that the dose makes the poison, carcinogenicity is generally regarded as having no threshold level. Although this no-threshold issue actually holds true only in the case of genotoxic carcinogens, deliberately adding a carcinogen to food is perceived in a different manner from adding an acutely toxic substance.

In light of this rather conflicting picture of labels, non-labels, and product restriction, risk communication becomes difficult — line markers containing TiO_2 are vanishing from shelves (because manufacturers don't want to be seen selling products labelled carcinogenic) and paint containing TiO_2 will receive extensive labelling by the new EU specific hazard statements while sweets containing E171 are still available. It will be hard to convey that the labelling pertains specifically to dry powders and expect consumers to be risk-educated enough as to not focus on the label carcinogenic and avoid TiO_2-containing products altogether, including sunscreens. Particularly the latter would be a prime example of regrettable 'avoidance behaviour' as TiO_2 in sunscreens has been a welcome technical addition after many organic compounds have been banned or are under scrutiny for environmental hazards and/or endocrine disruption.

Moreover, the proposed mechanism of carcinogenicity of TiO_2 is the induction of chronic lung inflammation due to an 'overload' of the lung's professional cleaning cells, the macrophages[13]. These cells in the deep lung, the alveolar region, cannot break down or digest the particles and accumulate so much material over time that it impedes their function. The macrophages' stress signalling and death causes inflammation of the surrounding lung tissue, eventually leading to tumour development[13]. This description of a mechanism is valid not only for TiO_2 but any material that can enter the deeper lung and cannot be sufficiently removed by macrophages. These are fine dusts in general, and particles of metals, metal oxides, plastics, and other pigments. Roughly a third of the food colourants registered under the European Union regulation Registration, Evaluation, Authorisation and Restriction of Chemicals[14] are flagged as available as nanomaterials in the EU market, hinting at the possibility of also exhibiting this mechanism. It needs to be stressed that those materials can have additional properties such as surface reactivity that can render them more hazardous. One possibility to address that might be a separate label conveying the risk of chronic inhalation exposure to dry powder leading to chronic inflammation and ultimately carcinogenicity, similar to, or expanding the classification of Specific Target Organ Toxicity — Repeated Exposure. Thereby, the risk would be clearly stated. Bulk material for food additives would still have to be labelled, but without falling into the same category as much more potent carcinogens. While not being an overall solution, this could provide a minimum classification for substances fulfilling the criteria of lung 'overload'.

Hazard versus risk

Currently, the CLP regulation is explicitly solely based on hazards and does not

accommodate exposure-based risks[2]. Therefore, the way the CLP regulation is currently handled should be re-assessed. For example, if the risk of experiencing the necessary high and chronic exposure is possible only in the professional environment, regulation could be implemented via occupational safety and health regulations. However, this has been ruled out for TiO_2 by the EU member states. Taking into account exposure even in a very simplified way could allow for such distinctions. Since the CLP regulation asks for evaluating only existing data[2], this could also cause reluctance to test materials and hence materials bearing other hazards not being labelled. If labelling is also meant for the uninformed consumer, it is in the interest of the regulators to present actual risks and not nebulous, mostly alarming hazards, without the need for reading the fine print. Otherwise, we are moving towards the real and fundamental issue of leaving the scientific grounds of well-founded risk assessment when it comes to public protection. Under the European Green Deal, ECHA and EFSA are supposed to move towards a process of 'one substance, one assessment'. TiO_2 might be a useful test case to design the process in a grounded way.

However, the suggestions above involve changes to the CLP regulation and/or the United Nations Globally Harmonized System, thus requiring lengthy, albeit worthwhile international negotiations. For now, it appears that the only choice is not to bring substances for which the data on inhalation carcinogenicity is solely based on effects in the lung 'overload' range into the process of harmonized classification for carcinogenicity. ❐

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Published online: 15 September 2020
https://doi.org/10.1038/s43016-020-00149-w

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Author contributions

All authors contributed equally to the conceptualization and writing of the manuscript.

Competing interests

The authors declare no competing interests.