Position of CAAP on the intention of the CLH Proposal to classify Titanium Dioxide as a potential carcinogen (short summary).

*The main goal of the classification process is to protect humans from an **identified** health concern.*

CAAP (Czech Association of Applied Photocatalysis) closely follows developments of the TiO_2 classification process and would like to drag attention to serious discrepancies in the Dossier's Proposal and RAC's adopted decision regardless its final status.

Obviously a carcinogenic substance should be classified, but a substance should not be declared as carcinogenic without adequate and robustly convincing evidence.

Although the RAC decision has been declared final, it seems inconsistent with ECHA principles thus CAAP must question the quality of the TiO_2 risk evaluation process.

Presuming carcinogenity of TiO_2 and creating speculative hypotheses around the issue when any direct evidence is lacking, is deemed to be a critical error in scientific analysis. CAAP understands there may not be TiO_2 experts in the RAC committee, though it insists that misinterpretation of the submitted data - instead of seeking for a professional expertise - is wrong.

CAAP fully shares the position of VDMI, TDMA, TDIC and the Association of Chemical Industry of the Czech Republic but in addition, the ECHA/RAC decision to classify TiO_2 as a potential carcinogen must be unfortunately considered **illegitimate** for following reasons:

1) **Misleading interpretation of the TiO_2 studies:**
   Position of the RAC: *In the opinion of RAC, the published results of the Heinrich et al. (1995) study are considered to be sufficiently reliable, relevant and adequate for the assessment of the carcinogenic potential of TiO_2: the main characteristics of substance identity were reported (P25 from Degussa, ~80% anatase and ~20% rutile, primary particle size 15-40 nm) and the variations in the exposure concentrations (7.2 mg/m³ for the first 4 months, followed by 14.8 mg/m³ for 4 months and 9.4 mg/m³ for an additional 16 months) are not considered to compromise the basic results in female rats tested. In an external validation of the study (based on OHAT methodology) the authors acknowledged a "high external and internal validity lending an overall high level of confidence in the available evidence" (Thompson et al. 2016)."*

   CAAP position:
   Heinrich et al. 1995 used Degussa P25 (today Evonic Aeroxide P25) for his inhalation study and very prolonged periods of exposure. RAC should have noticed that the pH of P25 is often lower than 3 and the loss on ignition at 800°C is typically 3-6wt %, which represent residual

hydrochloric acid on the surface of TiO_2 particles (MSDS of the particular Evonic Aeroxide P25 shows **pH 3.5** at **40 g / liter H_2O**).

This highly acidic P25 is commonly used in many of these studies because it is a readily available nano material (Oberdorster, Borm, Pott and many others). However, it is absolutely unsuitable for any fundamental TiO_2 lung overload study since the present residual hydrochloric acid stops the epithelium causing rapid overload and cementation of lungs and consequently permanent irritation. The concentrated HCl can be inordinately severe on the TiO_2 surface and is capable of irritation of lungs, as well as peptizing of proteins. **To interpret the HCl acid effect as a TiO_2 characteristic is indeed one of the most common errors in the studies**. In addition, the Heinrich's study is clipped by the composition of the experimental atmosphere, which contained not only acidic P25 dust but also 0.1ppm of extremely dangerous NOx and 0.1ppm of SO_2 (Table 3)**.** *This concentration of nitrogen oxides is several times higher than the legislative limits. EPA on this NOx concentration range – "The following groups should avoid prolonged outdoor exertion: people with lung disease, such as asthma, children and older adults; everyone else should limit prolonged outdoor exertion".*

The nonstandard fact that the experimental atmosphere contains NOx concentration far above the legal limits, and the awareness of the high acidity of P25 should have been obvious to RAC before making any decisions on TiO_2.

It is alarming that RAC was not able to recognize these errors during the Accordance Check stage and indeed trivializing the constructive advice later from several hundred public comments. **CAAP insists that Heinrich's study describes effects of the residual hydrochloric acid and acidic NOx atmosphere. This study does not provide any relevant information on carcinogenity of TiO_2 and therefore must be disqualified from the considerations.**

In the Xu study we see just another inadequate description of the tested material: "TiO_2 particles (rutile type, without coating; with a mean primary size of 20 nm) were provided by Japan Cosmetic Association, Tokyo, Japan." i.e., a similarly compromised study cannot be used as a proof of TiO_2 carcinogenity, either.

2) **Unreasonable intention.**

There is not a state of emergency to open this CLP issue in a view of a scheduled "Substance Evaluation" process under the REACH regulation process next year. This fact raises number of pertinent questions about the real purpose of the suspicious dossier's proposal. The main goals of this classification process were to protect humans from an **identifiable** health concern. CAAP insists there is no evidence of carcinogenity of TiO_2 in the dossier's submitted documents and

does not identify any health concern. Effect of acids and dust should not be misled for TiO2 carcinogenity.

By using the common sense, available statistics and a simple calculation model, CAAP experts can conservatively determine that the risk of **cancer to humans** from TiO_2 exposure might be lower than **1:10 000 000 000**. Thus it is the qualified and sustained opinion of the CAAP that a compound with such a low risk of health impact **should have never become a subject of classification efforts.**

3) **Effect of inert dust particles is common to ALL inert solid compounds. This effect cannot be interpreted as TiO_2 only specific characteristic.** RAC also mentions that inert dust cannot be a sole reason for carcinogenity of a compound (*RAC: "It is generally recognized that particle overload is not sufficient to explain alone a carcinogenic effect".),* but fails to identify the effects of the additives and residues in the experimental materials (*RAC's response on comments on carcinogenicity (animal data): RAC thoroughly discussed the reliability of the available TiO_2 inhalation studies. RAC in the end concluded that the Heinrich et al. (1995) study, supported by the results of inhalation studies with other PSLTs, is of adequate quality for classification purposes.*
Because of excessive exposure conditions RAC considered the Lee et al. (1985) study less adequate.)

CAAP note - Lee's own statements are**: *"no compound-related lung tumors were found in rats exposed to either 10 or 50 mg/m^3. In addition to excessive dust loading in the lungs of rats exposed chronically at 250 mg/m^3, the lung tumors were different from common human lung cancers in terms of tumor type, anatomic location, tumorigenesis, and were devoid of tumor metastasis. Therefore, the biological relevance of these lung tumors and other pulmonary lesions for man is negligible."***

Lee's publication as a **safe study** with the opposite interpretation of the findings than given by RAC was presented by Prof. Dr. Harald F.Krug at the TiO_2 Symposium in Paris in November 2016 (https://www.youtube.com/watch?v=8hi4COvdHSM&list=UU26oDdfuF5m_XAGji8D6_Gg&index=15#t=443.9269468 - 17th minute:).

CAAP opinion: Lee's study is a safe study. In Lee's study the TiO_2 is covered by dense, insoluble and inert Al_2O_3 surface treatment – typical example of inert dust, maybe with a small amount of dispersing agents. In this case the organism comes in contact with Alumina, not TiO_2, and therefore Lee's study cannot be used as a proof of TiO_2 carcinogenity. Additionally, the consensus about the highest acceptable concentration of dust used in the toxicological studies is 50mg TiO_2/m^3, as discussed in the TiO_2 Symposium in Paris in 2016, organized to bring more

light into the classification intention. The overload of lungs by 250mg/m^3 was excluded from consideration by consensus.

4) **Improper model for evaluation of TiO_2, misleading mixtures for a substance**

TiO_2 is a completely inert compound. As such, it does not practically make any chemical bonds. If any impurities are present next to TiO_2, they co-exist as a **heterogeneous mixture**.
A heterogeneous mixture cannot be considered as a single substance.

The RAC's definition of TiO_2 as a single substance with up to 17% impurities is not an adequate platform for consideration of carcinogenity of an inert compound and does not necessary change the fact that TiO_2 compound is harmless, while the impurities and additives may have significant adverse effects.

The patent purpose of the legislative is to protect the population. We can take for granted that pure, USP grade TiO_2 does not need any regulation while if the 83% purity rule is applied: i.e., one TiO_2 substance can be a rat poison, and another TiO_2 substance can be perfectly safe and even biocompatible.

Note: If the same principle were to be applied to water inhaled in a form of fog, analogous results as for inert dust and acidic dust may be observed (Environmental Health Perspectives Vol. 63, pp. 57-61, 1985; Potential Risks to Human Respiratory Health from "Acid Fog": Evidence from Experimental Studies of Volunteers by Jack D. Hackney, William S. Linn, and Edward L. Avol"). CAAP does not suspect ECHA to classify H_2O substance even though the exposure can even cause hyponatremia and kill people http://www.ncbi.nlm.nih.gov/pubmedhealth/PMH0001431/.

Similarly, inert compounds such as TiO_2 (inert dust) represent a baseline and should not be a subject to classification.

Important understanding is that following the ECHA's " Criteria for checking if substances are the same", CAAP sees logically much closer approach in the legislative created for inert catalysts (which TiO_2 is): ***Inorganic catalysts are regarded as mixtures. For identification purposes, component metals or metallic compounds should be considered as individual substances*** *(without specification of use).*
And further specification from the Criteria

- *Acids or bases and their salts shall be regarded as different substances.*
- *Individual salts (e.g. sodium or potassium) shall be regarded as different substances.*

CAAP suggests that correspondingly, impurities in the TiO_2 products (amines, acids, hydroxides, silica, alumina, polymers, surface treatments, etc.) must be reported separately and then toxicity/carcinogenity has to be calculated for the mixture.

CAAP position: Before a straightforward determination of toxicity and carcinogenity of pure TiO_2, the classification of TiO_2 interpreted by a model of a substance of up to 83% purity is totally unacceptable to CAAP.

5) **Inadequate scrutiny of the sources.** The decision to classify TiO_2 as a carcinogen has been made on **R2 and R3 rated** documents. Not a single **R1** document was present.
In our opinion, RAC did not follow the ECHA principles, giving excessive and unreasonable weight to doubtful studies and reviews, rather than taking into account numerous TiO_2 studies, which were run in compliance with the *Test Methods Regulation (Council Regulation (EC) No 440/2008) that contains all the test methods previously included in Annex V to Directive 67/548/EEC or to OECD Test Guidelines (or other standards like CEN, ISO, ASTM, OSPAR methods, national standard methods), and in compliance with the principles of GLP or equivalent standards. Furthermore, new ecotoxicological and toxicological tests shall be carried out in compliance with the principles of GLP (see Directive 2004/10/EC) or equivalent international standards.*

6) **When RAC makes any decision on strategic substances, the amount of qualified scrutiny work and its quality should be adequate to the importance of the compound and possible consequences!**
It is important to highlight that ***not one*** *of the documents used as a base for the decision, would pass the* DANA's criteria checklist (the updated DaNa Literature Criteria Checklist "Methodology for selection of publications", http://www.nanoobjects.info/files/methodik/DaNa_criteria_checklist_2016tox_en.pdf).

7) **RAC has trivialized – and disregarded – prevalent statistics and relevant information** provided by TiO_2 manufactures and processing companies received during the **public consultations** period, stating, rather**:** "Overall, references submitted during public consultation do not constitute new data and do not impact the CLH proposal", whereas CAAP views this information as a collection of valuable statistics additional to the existing epidemiological studies.

RACs rejection of these comments studies, statistics supplemental data, and even detailed analyses of the CLP proposal (totaling over 500 provided responses!), received from the top experts and the real world industrial leaders as "inadequate". It can even be viewed as extremely overconfident especially, after so many errors are obvious in the logic of the proposal as well as in the evaluation process. Also alarming in the decision are all the speculative formal reasonings and justifications as to why the RAC does not intend to establish any constructive dialog with the world-class experts in the field, choosing rather to force its preconceptions through legal mechanics instead of seeking consensus from peers, including TDMA experts and observers.

This position held by the RAC committee, indeed its state of mind, are such that urgent focus on this troubling episode is something that requires immediate attention.

Further, the RAC is supposed to be a group of responsible experts able to solve complex issues and make qualified decisions. CAAP agrees that these people should not, and must not be influenced by any outside endeavors or means when making their decisions; this however does not preclude that they are not accountable for their decisions.

Clearly, the public reaction to the classification intention was practically uniform. In the opinion of the CAAP, it is not possible to ignore and trivialize 500 public comments that provide valuable statistics on occupational health data from their workplaces: additional solid evidence to already sound epidemiologic studies.
No decision on TiO_2 carcinogenity should be made before all questions regarding reliability of the studies are solved and **a broad consensus** on the carcinogenity issue has been established.

8) **The high oral and dermal loads without any health impact underline the absolutely inert properties of TiO_2.**

9) **It is not tolerable today to consider any toxicological study with only partial information on TiO_2 purity, chemical properties and physical characteristics**, especially today, when universities and privately held companies possess high-tech equipment and almost unlimited capabilities of chemical and physical analysis and databases which allow precise descriptions of experimental materials.

10) **On strategic compounds, sufficient time should be provided** for public comments and the whole procedure. Time spent on the evaluation, discussions and expert opinions should be adequate to the importance of the compound allowing proper understanding of the problem that may need careful studying of even thousands of pages of technical literature.

11) CAAP questions who is interested in pushing this **clearly political and contentious issue** rendering a debilitating affect on EU competitiveness, economical strength, prosperity, product quality and ability to produce energy via this extremely narrow, unprofessional, prejudicing and alibistic expertise? Could RAC's response be prevailingly political with a number of trivializing and equivocal hypothesis rather than be based on serious technical information? Can we accept that the formal part of the process is not based solely on facts and can gain more importance than the factual data?

POSITION OF CAAP

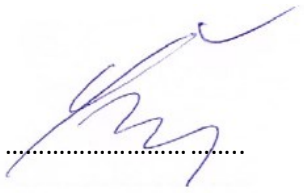
CAAP does not find any supporting evidence for classification of TiO_2 as carcinogen in the proposal and requests reverting the CLH decision on TiO_2 back to non-classified. ECHA should dismiss any TiO_2 classification proposal in the future, unless solid, reliable, proven and reproducible evidence is provided. Reliability of such evidence should be as solid as the statistics from one century of producing, processing and exposure of TiO_2 and the considerations as careful as the importance of the strategic compound and weight of the potential consequences.

This TiO_2 case clearly demonstrated drawbacks of the legislative system by which, any compound, including water could be classified.

Different compounds have different importance and accordingly, the evaluation process on strategic compounds should be conducted with exceptional care and sufficient time focusing on the reliability of the submitted information and attention to all complex and important details during the accordance check. Further, CAAP insists that ECHA/RAC was supposed to perform the Accordance check and return the dossier's submittal for the lack of relevant information.

Further CAAP suggests revision of the classification procedure, provided that a constructive, complex, transparent and factual consideration process has to be delivered, to avoid abuse of the ECHA/REACH classification system. Otherwise it could be easily harmed and abused by a foreign power, lobby groups, influential political, business or religious groups and even bureaucratic irrationality, weakening the EU, its economy as well as its political and moral might.

For CAAP In Prague, 10 November, 2017



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