Position Paper on Titanium Dioxide

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MedPharmPlast Europe, a sector group of the European Plastics Converters, represents companies involved in the whole value chain of plastic medical devices and pharmaceutical packaging in Europe.

There are currently at least 275 light-sensitive oral prescription drugs[1] and over 300 light-sensitive injectable medicinal products [2] . These drugs thus require pharmaceutical packaging that is able to prevent the passage of light, particularly in the spectrum 290 to 450nm to prevent degradation of the pharmaceuticals. This requirement is defined in US Pharmacopeia <671> and it critical for obtaining market authorization for light-sensitive pharmaceuticals. To reduce transmission colours that filter (e.g. amber) need to be added. In the case of transparent packaging or in other cases an opacifying agent needs to be added to the polymer. The number of drugs with a need for protection is increasing.

The European Pharmacopoeia's section 3.1 on materials used for containers refers to just one opacifying agent: Titanium Dioxide. Although the titanium dioxide referred to in the European Pharmacopeia monograph is ultra-high purity used in drug formulation, whereas titanium dioxide used in plastics have coatings to make them compatible with the polymer and process, **there is a wide use of titanium dioxide in pharmaceutical containers**. In addition coloured plastics used for medical container closures and a wide range of medical devices often use titanium dioxide in the formulation of the colour. This is to provide increased opacity and a stable base colour. Thereby avoiding to add higher quantities of expensive pigments and allowing less materials to be used. Therefore titanium dioxide represents a widely used and resource saving solution.

In all cases described above, the titanium dioxide is pre-dispersed within the matrix of a melted polymer. On cooling the particles are encapsulated and cannot escape. The principle of encapsulation is well understood under REACH, the scenario for particles to escape is extremely unlikely[3].

MedPharmPlast Europe is concerned over the investigation by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) which could lead to a classification of titanium dioxide as a carcinogen (Carc. 1B). Such a classification would have a number of consequences:

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[1] King A. Light-Sensitive Oral Prescription Drugs. Hospital Pharmacy. 2009;44(12):1112-4Allison
[2] Light-sensitive injectable prescription drugs. Hosp Pharm. 2014;49(2):136-63.
[3] OECD. Series on Emission Scenario Documents. Emission Scenario Document on Plastic Additives 2009

- There would be a perception by users in the market that alternative substances would need to be found, involving a change management process, validation studies lasting many years, and many millions of Euros in additional costs. **This would in fact increase the risk to patients, because it is unlikely that other materials would have the same history in use, and therefore less well studied.**
- There would be an impact internationally, since the Global Harmonization Task Force (GHTF) tries to harmonize assessment of materials for medical device and pharmaceutical regulations, and this would be a divergence.

The current CLP dossier submitted to ECHA focuses on TiO2 dust. The dossier contains no evidence that exposure to Titanium Dioxide dust leads to cancer in humans. Only two studies show a link between inhalation of TiO2 dust and tumorigenesis in rats, a species uniquely susceptible to this type of lung overload toxicity[4].

The histological evidence of the first investigation by Lee et al. was re-examined in 2006 with new diagnostic criteria by Warheit and Frame, which led to the conclusion that in the highest exposure group only one out of 100 rats developed cancer, which cannot be considered statistically significant.

The second study was designed to determine if diesel soot was toxic due to the presence of organic chemicals – the ruling hypothesis at the time – in the diesel particles or whether the presence of particles themselves is toxic. Titanium Dioxide was included as a control; as it does not contain any organic chemicals and its particles have similar dimensions as the diesel soot. The authors demonstrated that diesel soot toxicity in rats is indeed related to the presence of particles in the rat lung, as rats developed similar rates of cancer when exposed to diesel soot, carbon black particles, and titanium dioxide particles. Therefore the authors concluded that: "Obviously, there seems to be a particle-specific carcinogenic effect in the rat lung."[5]

The CLP legislation which is currently being considered is a substance specific policy instrument, while the scientific evidence shows that any potential toxicity is driven by the inhalation of dust particles. Several countries have already introduced occupational exposure limits (OELs) for dust[6], which as recent research suggests has decreased exposure significantly[7].

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[4] ECETOC (2013) – Poorly Soluble Particles / Lung Overload: Technical Report No. 122

[5] Heinrich et al (1995) Chronic inhalation exposure of Wistar rats and two different strains of mice to diesel engine exhaust, carbon black, and titanium dioxide

[6] Based on GESTIS database search (5 May 2016): Austria, Belgium, Canada, Denmark, Finland, France, Germany, China, Spain, Sweden, Hungary, Ireland, Singapore, and Switzerland.

[7] Creely KS, Cowie H, Van Tongeren M, Kromhout H, Tickner J, Cherrie JW. Trends in inhalation exposure--a review of the data in the published scientific literature. Ann Occup Hyg. 2007;51(8):665-78.

MedPharmPlast Europe contacted the primary author prof. dr. dr. Uwe Heinrich of this study and he confirmed that:

- Rats are uniquely susceptible to "lung overload"
- If a toxic effect exists it is due to the particle not the substance itself.
- In his opinion an OEL for dust, respirable dust and ultrafine dust (<100nm) would be a better solution to cover the risks associated with this particular issue.

Therefore, MedPharmPlast Europe believes that, as CLP legislation is a substance specific policy instrument, it would not be appropriate to classify the entire substance based on an effect seen with particle of all low solubility substances. An EU-Binding OEL for all dust would be more appropriate to cover this potential risk arising from dust without negatively affecting the use of titanium dioxide.