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COMMITTEE OF EXPERTS ON THE TRANSPORT OF DANGEROUS GOODS AND ON THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS

Sub-Committee of Experts on the Globally Harmonized System of Classification and Labelling of Chemicals

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UPDATING OF THE THIRD REVISED EDITION OF THE GLOBALLY HARMONIZED SYSTEM OF CLASSIFICATION AND LABELLING OF CHEMICALS (GHS)

Health hazards

Proposal for the review of Chapter 3.9.2 to avoid scientifically unjustified classification of poorly soluble particles for specific target organ toxicity following repeated exposure on the basis of lung-overload related inflammation responses in the rat

Transmitted by the International Council on Mining and Metals (ICMM) and the European Chemical Industry Council (CEFIC)[1]

Introduction

1. Chapter 3.9.2 of the Globally Harmonized System of Classification and Labelling of Chemicals (GHS) provides the definitions, criteria and guidance to classify substances that produce specific target organ toxicity arising from repeated exposure. It defines that classification depends upon the availability of reliable evidence that a repeated exposure to the substance has produced a consistent and identifiable toxic effect in humans or that toxic effects which have been observed in experimental animals are relevant for human health.

[1] In accordance with the programme of work of the Sub-Committee for 2009-2010 approved by the Committee at its fourth session (refer to ST/SG/AC.10/C.4/32, Annex II and ST/SG/AC.10/36, para. 14)

2. Sections 3.9.2.3 to 3.9.2.5 specify that the classification for specific target organ toxicity following repeated exposure has to be determined by expert judgement by taking all evidence into account. This includes information from human incident reports, epidemiology, and studies conducted in experimental animals. The information required to evaluate specific target organ toxicity comes either from repeated exposure in humans or from studies conducted in experimental animals. For respiratory effects after inhalation, the standard animal studies in rats or mice that provide this information are 28 day, 90 day or lifetime studies. Following current guidelines, positive results in either humans or animal studies will drive the STOT classification.

3. Section 3.9.2.9 provides guidance values to assist with classification for respiratory effects after inhalation based on the results obtained from studies conducted in experimental animals. In addition, for the interpretation of particle inhalation studies conducted in experimental animals, the following guideline values are provided.

Table 1: Extract from tables 3.9.1 and 3.9.2 (GHS Rev.3) regarding guideline values for assisting with the classification of particle inhalation studies in experimental animals

Study type	Species	Units	Category 1		Category 2	
			90-day	28-day	90-day	28-day
Inhalation, dust/mist/fume	Rat	mg/l/6h/d	≤ 0.02	≤ 0.06	≤ 0.2	≤ 0.6
		mg/m^3/6h/d	≤ 20	≤ 60	≤ 200	≤ 600

4. The majority of the data on the respiratory effects of inhaled poorly soluble particles stems from rat inhalation studies[2]. The rat has, however, been shown to be more sensitive than humans or other rodent species to exposure to poorly soluble particles. Under particle exposure conditions equalling the guideline values provided in table 1, virtually any poorly soluble particle would lead to a lung overload-related inflammatory response in rats. Therefore, according to the criteria presented in chapter 3.9.2, these particles will be classified for specific target organ toxicity following repeated exposure, even if humans are not expected to have such a response at equivalent exposure levels[3]. Applying strictly the existing guideline values to results obtained from inhalation studies in the rat without taking into account the rat specific responses to inhaled poorly soluble particles would not allow the distinction between chemical-specific and inert particle-induced toxicity.

[2] ILSI Risk Science Institute (2000). The relevance of the rat lung response to particle overload for human risk assessment: A workshop consensus report. Inhalation Toxicology 12, 1-17.

[3] Animal inhalation studies with poorly soluble particles are usually conducted with a fairly homogenous aerosol of small particle size (Mass Median Aerodynamic Diameter (MMAD) of 1.5 – 3 µm) to maximise the deposition from the exposures in animals and therefore the delivered dose to the animal. In occupational settings, workers can be exposed to dusts with MMADs of up to 100 µm. Any comparison between animal poorly soluble particles dose-response data and occupational exposures needs to take into account differences in particle size, deposition and clearance between animals and humans.

5. The aim of this document is to highlight the issues associated with the application of the GHS criteria and guideline values for specific target organ toxicity following repeated exposure to inhaled poorly soluble particles of low cytotoxicity and to request the formation of a working group of experts to review and refine the current criteria and guideline values. Guidance development by the European Union for the implementation of the GHS (Draft REACH Implementation Project (RIP) 3.6 guidance), noted that the relevance of lung overload in animals to humans is currently not clear and is subject to continued scientific debate. Therefore it is timely that this issue is reviewed. Key considerations in the inhalation toxicology of poorly soluble particles of low cytotoxicity.

6. Numerous subchronic or chronic experimental inhalation studies have been conducted with poorly soluble particles such as titanium dioxide, coal dust, carbon black and talc that are considered of low cytotoxicity. Typical particle exposure concentrations in these studies ranged from 1 to 30 mg/m^3, exceptionally even up to 250 mg/m^3 in a two-year titanium dioxide inhalation study. The retained particulate lung burdens were high, reaching several milligrams per gram of lung tissue. At these high exposure levels, inflammatory responses, altered particle kinetics, altered morphology and finally chronic disease including fibrosis were observed which are indicative of lung overload caused by general particles rather than a specific toxicity effect of the substance in particle form[4].

7. For chronic inhalation of poorly soluble particles, particle overload is a consequence of excessive exposure that results in a retained lung burden of particles that is greater than the steady state burden predicted from the deposition rates and normal clearance kinetics of particles inhaled during exposure. It seems not to be particle type specific and can occur with any poorly soluble particle with low cytotoxicity. The hallmark of particle overload is impaired alveolar clearance which, in rats exposed to poorly soluble particles, is associated with altered macrophage function, pulmonary inflammation, centri-acinar interstitial and alveolar accumulation of particles, and inflammation-induced epithelial cell proliferation[5].

8. The concept of lung overload applies specifically to poorly soluble particles with low cytotoxicity. Other, more cytotoxic particles affect alveolar macrophage-mediated clearance as well but at much lower lung burdens (e.g., crystalline silica). Thus, not all impairment of alveolar macrophage-mediated clearance should be viewed as a condition of particle overload[6, 7].

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[4] Oberdörster G. (1995). Lung Particle Overload: Implications for Occupational Exposures to Particles. Regulatory Toxicology and Pharmacology 27, 123-135.

[5] ILSI Risk Science Institute (2000). The relevance of the rat lung response to particle overload for human risk assessment: A workshop consensus report. Inhalation Toxicology 12, 1-17.

[6] Oberdörster G. (2002). Toxicokinetics and effects of fibrous and non-fibrous particles. Inhalation Toxicology 14, 29-56.

[7] Mauderly, J.L. (1997) Relevance of particle-induced rat lung tumours for assessing lung carcinogenic hazard and human lung cancer risk. Environ. Health Perspect. 105 (suppl. 5), 1337 – 1346.

9. A number of chronic inhalation studies have been conducted in rats to assess the effects of poorly soluble particles including talc, titanium dioxide and carbon black. These studies demonstrated that chronic inhalation of poorly soluble particles can result in pulmonary inflammation, fibrosis, or epithelial hyperplasia and in some instances adenomas or carcinoma in the peripheral lung of rats. The development of lung tumours occurs frequently in rats under lung overload conditions[8], while other rodents, such as mice and hamsters, or humans did not develop lung tumours under similar exposure conditions of lung overload from poorly soluble particles. The evidence to support this contention points to the uniqueness of a very specific patho-physiological process operating in the rat, i.e. the inability of rats to effectively clear the lungs from particles and a sustained inflammatory process. These species differences are not confined to the development of tumours. A range of studies suggested that rats exhibit greater pulmonary inflammation, fibrotic and epithelial hyperplastic responses to particles than hamsters or mice[9,10,11].

10. The differential response of rats to poorly soluble particles can be explained because the distribution of the retained particles within the lung compartments is different between species. As long ago as 1969, Snipes reviewed information suggesting that during chronic inhalation exposure, particles are retained to a greater degree in interstitial locations in lungs of non-human primates and dogs than in lungs of rats and hypothesized that the interspecies differences in particle location might contribute to corresponding differences in tissue response[12]. This difference combined with the fact that human macrophages have five times the volume of rat macrophages is now considered to account for the tendency of rats to respond to poorly soluble particles with more chronic inflammation and epithelial responses compared to humans[13].

11. In summary, the current criteria and guideline values for the classification following repeated exposure on the basis of rat inhalation studies as set out in Chapter 3.9.2 when related to poorly soluble particles of low cytotoxicity for specific target organ toxicity should be re-considered. These should aim to better distinguish between poorly soluble particles, having toxicity effects only in rats at high doses as a result of lung overload and other particles with intrinsic cytotoxicity. Factors to take into account include:

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[8] Mauderly, J.L. (1996). Lung Overload : The Dilemma and Opportunities for Resolution. Inhalation Toxicology 8, 1-28.

[9] Carter, J.M. *et al*. (2006). A comparative dose-related response of several pro- and anti-inflammatory mediators in the lungs of rats, mice and hamsters after subchronic inhalation of carbon black. JOEM 48, 1265 – 1278.

[10] Bermudez *et al*. (2002). Long-term pulmonary responses of three laboratory rodent species to subchronic inhalation of pigmentary titanium dioxide particles. Toxicol. Sci. 70, 86-97.

[11] Bermudez *et al*. (2004). Pulmonary responses of mice, rats and hamsters to subchronic inhalation of ultrafine titanium dioxide particles. Toxicol. Sci. 77, 347-357.

[12] Snipes M.B. (1996). Current information on lung overload in non-rodent mammals: contrast with rats. Inhalation Toxicology 8(Suppl.), 91-109.

[13] Oberdörster G. (1995). Lung Particle Overload: Implications for Occupational Exposures to Particles. Regulatory Toxicology and Pharmacology 27, 123-135.

(a) The majority of the inhalation toxicity information stems from repeated inhalation exposure studies in rodents, predominantly in rats;

(b) The rat has been shown to be particularly susceptible to particle exposures because of its inability to effectively clear the lungs ("lung overload") resulting in a sustained inflammatory process;

(c) The exposure conditions typically achieved in rodent inhalation experiments do not reflect human exposures occurring at the workplace or elsewhere;

(d) It has been demonstrated with reasonable certainty that lung overload conditions are not relevant for human health and, therefore, results based on such data alone do not justify classification.

12. Failure to consider the species-specific effects would lead to classification of virtually any poorly soluble particle. Applying strictly the existing guideline values to results obtained from inhalation studies in the rat without taking into account the rat specific responses to inhaled poorly soluble particles would not allow the distinction between "chemical-specific" and "particle-induced" toxicity.

Request

13. It is requested that a specific working group of experts on the inhalation toxicology of poorly soluble particles be established to review and further refine the current criteria and amend the guideline values to take into account the specific issues that relate to the classification of particles for specific target organ toxicity following repeated exposure.

14. It is proposed, that the Chapter 3.9.2 recognizes the rat-specific phenomenon of "lung overload" for the inhalation toxicity of poorly soluble particles of low toxicity and that classifications for specific target organ toxicity following repeated exposure should not be based on lung overload related responses in the rat.
