BeST
Beryllium Science & Technology Association

Current Scientific State on the Toxicology of Beryllium Metal

Summary

According to REACH, classification for the individual substance beryllium metal is required, and thus the classification together with beryllium compounds is not compliant with the legislative requirements. Documented rationales for the classifications of beryllium and beryllium compounds in the EU are not available. Only summary records of meetings of various institutions are available and thus a documented rationale for the existing classification does not exist. Consequently, there are a number of uncertainties to assess the basis for the current classification. Additionally, it is not reproducible what studies may have been considered or were not considered for classification, and which of the data can be considered reliable using the quality standards that exist today.

The REACH legislation is designed to provide safety, health, environmental and use information about chemical substances to European Chemicals Agency (ECHA). Accordingly, a consortium of beryllium producers engaged Harlan Laboratories Ltd. to address the testing requirements of REACH for the purposes of registering beryllium metal. The test results clearly indicate that beryllium metal differs significantly from beryllium salts in regard to physico-chemical properties. This is generally being demonstrated in toxicity studies of other metals as well. The genotoxicity tests in vitro using beryllium metal powder, covering gene mutation, chromosome aberration, DNA repair and its inhibition, did not reveal any genotoxic potential for beryllium metal when extracted under simulated lung conditions. Additionally, a quality analysis of all the animal studies in the literature clearly suggests that the carcinogenicity data in other species is scarce. The toxicological studies based on beryllium metal carcinogenicity are very much focused on carcinogenicity in the rat and there is strong support for the fact that the rat is not an ideal model for this endpoint for poorly soluble particulate substances due to special lung reactions. It should also be noted that the testing of beryllium metal also clearly indicated that Be metal should not be classified as a skin irritant, an eye irritant, an acute inhalation toxin, a skin sensitizer, or orally toxic as it is today. The current classification of beryllium metal is not in line with current scientific studies and needs to be revised.

Specific Toxicity Study Results

Human Epidemiology

Epidemiological data developed in the United States is very weak and subject to statistical flaws, inadequate mathematical manipulation of the data and does not comport with studies in Europe. For example, an analysis of the UK Beryllium Registry (Williams, W. J. 1996) that includes all cases of chronic beryllium and expected beryllium disease found no cancer related deaths among the 69 deaths associated with exposure to beryllium. Additionally, in a publication by the German/Austrian Cancer Society (DK, 2009) no cases of lung cancer were listed in the beryllium disease registry. This report assessed occupational disease cases from 1978 to 2003. Furthermore, The Industrial Injuries Advisory Council Position Paper 27,

December 2009 Beryllium and Lung Cancer“ states: “The main epidemiological evidence on occupational risks of lung cancer in beryllium-exposed workers derives from large US studies of beryllium process workers and of a US national register of beryllium workers. Although there have been several research reports, the evidence base is restricted to only a few cohorts with relevant data. The Council found no UK-relevant studies to inform its inquiries.” “The Council has concluded that at present there is insufficient evidence to recommend that lung cancer in relation to beryllium should be added to the list of prescribed diseases. ” A critical analysis of the literature clearly demonstrates that there is not sufficient evidence to conclude that beryllium causes cancer in humans even at the high doses that existed decades ago in production facilities in the United States which are not even relevant to activities within the EU.

Animal Studies

An extensive literature search was conducted and screened for beryllium metal as the substance of interest, and inhalation as the relevant route of exposure to animals. Five studies addressing carcinogenicity after lung exposure to beryllium metal were. One additional study with beryllium metal was identified (Hueper et al., 1954), but not considered to add relevant information for risk characterization under human exposure conditions due to the unphysiologic routes of exposure in this study (intramuscular or intrapleural injection) and thus not included. No carcinogenicity study with oral or dermal exposure to beryllium metal was identified. The studies were evaluated for quality and reporting by the system proposed by Klimisch et al. (Klimisch et al., 1997). None of the identified studies were conducted under GLP and of the 1531 studies screened only one of the individual studies was designed and reported in a way that could be evaluated as “reliable with restrictions (2)” according to the system proposed by Klimisch. Another study was published in smaller fragments in the scientific literature in form of abstracts of oral presentations or posters, experimental- and review articles. Although the individual publications do not report sufficient details to allow evaluation of the data quality, the overall information provided in the publications provides enough details to convince that the study was performed under well controlled conditions and that the results are reliable. The other publications were “not assignable (4)” under the Klimisch system, as methods and results were only reported in abstract form without description of any experimental details or tabulation of individual data. Despite the overall low quality of reporting, application of a weight-of-evidence approach leads to the conclusion that the rat shows a robust carcinogenic response to inhaled beryllium metal even after single exposure. Experimental attempts were made in the study program to reproduce this effect in other species. No carcinogenic responses in mice and guinea pigs could be demonstrated (Nikula et al., 1995; Schepers et al., 1961; Finch et al., 1995 and 1998a/b) and only challenging the situation by using a sensitive animal model (p53 knockout mice or A/J mice with a massive lung tumor background) led to a weak positive response to inhaled beryllium metal. The general predictivity of rodent carcinogenicity testing for the human situation is not satisfactory. Alternative methods are currently under evaluation, but have not been validated or accepted as standard methods. Systematic review of the carcinogenicity potency database (Gold et al., 1998) revealed that about 50% of the chemicals tested for carcinogenicity in rodents gave positive results in at least one species. Compared to the data obtained by epidemiology and occupational health monitoring, there is a clear indication that there is a high amount of false-positive results. Alternative methods (e.g. carcinogenomics, *in vitro* methods) are currently being evaluated (Vinken et al., 2008) and are promising to show a better correlation to the human situation than the rodent carcinogenicity testing, but until

the validations are finished, it remains unclear which tests give better predictions for the human situation.

Toxicity Testing Results

The toxicity of soluble metal compounds is often different from that of the parent metal. Since no reliable data on acute toxicity, local effects and mutagenicity of beryllium metal has ever been generated, beryllium metal powder was tested according to the respective OECD guidelines. Acute oral toxicity of beryllium metal was investigated in rats, and local effects on skin and eye in rabbits. Skin sensitizing properties was investigated in guinea pigs (Maximization method). Basic knowledge about systemic bioavailability is important for the design of genotoxicity tests on poorly soluble substances. Therefore, it was necessary to experimentally compare the capacities of beryllium chloride and beryllium metal to form ions under simulated human lung conditions. Solubility of beryllium metal in artificial lung fluid was low, while solubility in artificial lysosomal fluid was moderate. Beryllium chloride dissolution kinetics were largely different, and thus metal extracts were used in the *in vitro* genotoxicity tests. Genotoxicity was investigated *in vitro* in a bacterial reverse mutagenicity assay, a mammalian cell gene mutation assay, a mammalian cell chromosome aberration assay, and an unscheduled DNA synthesis (UDS) assay. In addition, cell transformation was tested in a Syrian Hamster Embryo Cell assay, and potential inhibition of DNA repair was tested by modification of the UDS assay. Beryllium metal was found not to be mutagenic or clastogenic based on the experimental *in vitro* results. Furthermore, treatment with beryllium metal extracts did not induce DNA repair synthesis, indicative of no DNA damaging potential of beryllium metal. A cell transforming potential and a tendency to inhibit DNA repair when the cell is severely damaged by an external stimulus was observed. Beryllium metal was also found not to be a skin or eye irritant, not to be a skin sensitizer, and not to have relevant acute oral toxic properties.