Minority opinion regarding the 'no classification' of methylmercuric chloride (MMC) for germ cell mutagenicity

Betty Hakkert, April 2017

The minority opinion regarding this 'no classification' is the following:

Minority view
The reason presented in the opinion to go for 'no classification' is that, whereas MMC clearly has mutagenic potential in vitro, the available in vivo data are insufficient to demonstrate activity in vivo, and no firm conclusion can be drawn from the available information in humans.

I do not agree with the argument that the available in vivo data are insufficient to demonstrate activity in vivo. There are three positive *in vivo* studies with various species and cell types. Although two of these studies are stated to have several shortcomings, the study in Syrian Hamsters with intraperitoneal application is stated in the ODD to be well conducted, with the inclusion of positive and negative controls and the use of a sufficient number of animals. This study shows a significant increase in frequency of hyperploid in oocytes of treated animals. Despite these results it is stated in the opinion that: "… *it is not possible to conclude from this study whether exposure to MMC by a physiological route would have produced a similar positive result, but it does seem to support the results seen in the in vitro studies, showing that MMC has the potential to damage mammalian chromosomes*". I have serious problems with this reasoning, as in the opinion it is also concluded that the oral absorption is almost 100%, and that ´... *this substance is readily taken up and distributed in the body, as seen from the studies of other toxicological endpoints*". Based on this, there is in my view no reason to doubt whether the results seen in the intraperitoneal study are also relevant for the physiologically more relevant oral route.

So, in my view all the criteria mentioned in CLP Guidance 3.5.2.4 ("If there are positive results from at least one valid in vivo mutagenicity test using intraperitoneal application, or from at least one valid genotoxicity test using intraperitoneal application plus supportive in vitro data, classification is warranted. ") have clearly been met in the present dossier. There is further ssupportive evidence from five epidemiology studies, showing positive correlations with methylmercury in hair and/or blood and changes in lymphocytes (amongst others chromatid breaks). Although due to several shortcomings these studies cannot be used on their own, I am of the opinion that these studies do not contradict but rather support the positive findings in well conducted in vitro studies and the in vivo study in Syrian Hamsters.

Based on the above, I disagree with the conclusion of NO classification for germ cell mutagenicity as it is not in line with the CLP criteria/guidance. I am of the opinion that the substance should at least be classified as a Category 2 mutagen (as initially proposed by the Dossier Submitter and in line with three commenting Member States). In view of the effects seen in oocytes even a classification as a Category 1B mutagen could be considered.