

The NiPERA News Bulletin is published in electronic form to inform NiPERA's members of our regulatory initiatives, presentations, research updates, etc. Copies of the document are available in the password protected Members Area at: <http://www.nipera.org> or by Faxing NiPERA at: U.S.A. 919-544-7724.

CONTENTS

Regulatory Initiative	<input checked="" type="checkbox"/>
Staff Presentation	<input type="checkbox"/>
Research Update	<input type="checkbox"/>
Meeting Minutes	<input type="checkbox"/>
Other	<input type="checkbox"/>

Danish EPA Accepts Oral Carcinogenicity Study as Conclusive Evidence that Nickel is not a Systemic Carcinogen

The classification proposal for nickel sulphate, nickel dichloride, nickel dinitrate, and nickel carbonate carcinogenicity as Carcinogen Category 1; R49 was agreed at the September 2004 TC Classification & Labeling meeting and has been included in the draft 30th ATP. At the September 2004 meeting, there was a discussion as to whether there was sufficient negative evidence of carcinogenicity by other routes of exposure for these nickel compounds to justify limiting the classification to the inhalation route of exposure. The TC Classification & Labeling ultimately concluded that the R49 classification, limiting the carcinogenic effect of the compounds to inhalation exposure, was justified. This conclusion was predicated upon the negative outcome of an oral carcinogenicity study sponsored by NiPERA which was underway at that time. Industry was instructed to submit the results of the oral carcinogenicity study of nickel sulfate hexahydrate upon completion of the study.

The NiPERA-sponsored oral (gavage) carcinogenicity study on nickel sulphate hexahydrate was completed in July 2005 (see NiPERA News Bulletin No. 142). This study demonstrated that daily oral administration of nickel sulfate hexahydrate to male and female Fischer 344 rats for up to two years did not significantly increase the occurrence of tumors at doses up to 50 mg/kg/day (11 mg Ni/kg/day), which was the highest dose tested. This dose is more than 2000 times higher than the human average daily nickel intake. The animals' body weight gain was reduced by at least 10% at the highest dose levels for males and females, which was statistically and biologically significant. This effect alone demonstrates that the maximum tolerated dose (MTD) was conclusively achieved in this study.

The Danish Rapporteur received the results from this study in July 2005. On October 18, 2005 the Danish EPA submitted a letter to the TC Classification & Labeling concluding that "...we <the Danish EPA> can agree with the conclusion that the study is convincingly negative. In our view, this study provides confirmation that the conclusion agreed by the TC NES in September 2004 <R49> is fully justified." The letter from the Danish EPA to the TC Classification & Labeling was distributed to the Member States on October 19, 2005 with the offer to provide the oral carcinogenicity study report, if requested. If no contrary response is received by the TC Classification & Labeling, the R49 designation which constrains the Carcinogen Category 1 classification to inhalation exposure will be finalized upon publication of the 30th ATP later this year.

The Danish review of the oral carcinogenicity study on nickel sulphate hexahydrate provides the first regulatory opinion of the usefulness of the data derived from that study. Their conclusion that the study is "...convincingly negative" supports the industry interpretation and should help in additional reviews of this study by the U.S. EPA Office of Water, the California EPA, and the WHO for their consideration in setting guidelines for nickel in drinking water. The results of this study will ensure that a nickel limit value in drinking water will not be zero, which is required for an oral carcinogen, but instead will be based on other toxicity endpoints (e.g., reproductive toxicity in animals).