Rhodia

HS&E CORPORATE SERVICES
Toxicology Department

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Dr. Mary Wolfe
NTP Board Executive Secretary
NIEHS
P.O. Box 12233, MD A3-07
Research Triangle Park, NC 27709

Subject: Comments on nomination of sodium metasilicate for toxicological studies

Dear Dr. Wolfe:

As I indicated in my e-mail message to you earlier today, the identical comments below were mailed to Dr. Scott Masten of NIEHS/NTP earlier this month.

Rhodia Inc., the U.S. subsidiary of Rhodia, one of the world's leading specialty chemical companies, wishes to submit comments on the nomination of sodium metasilicate (CAS # 6834-92-0) for proposed subchronic inhalation toxicity testing and hypersensitivity testing via dermal or inhalation routes of exposure, which was published in the **Federal Register** of June 12, 2002 (67 FR 40329). Rhodia manufactures sodium metasilicate in countries other than the United States, and sells the chemical both in the United States and elsewhere.

Rhodia Inc. believes that both categories of testing being proposed are unnecessary. In the case of the nomination for proposed subchronic testing, please note that Rhodia in France is part of a consortium supporting several silicates (sodium, potassium and sodium meta-) under the ICCA High Production Volume Chemical testing initiative. As you are aware, the ICCA initiative is similar to the US EPA HPV initiative, but it is more comprehensive in its data requirements than the US program. Subchronic toxicity testing is one among the many toxicity studies encompassed by the ICCA HPV program, so data that address the endpoints being sought will be forthcoming, summarized and posted for public review in the near future. It is understood that a draft of the dossier is under review by the member companies of the consortium.

Even without the forthcoming release of the ICCA HPV dossier on the three silicates, the literature review prepared for the NTP should make it abundantly clear that adequate data exist to predict the subchronic effects of exposure to sodium metasilicate. The kidney has been identified as the sole internal target

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for toxicity, apart from the chemical's potential for contact eye, skin and respiratory tract irritation. Given the long history and wide-spread use of the product, it would seem highly unlikely that an NTP-sponsored study would reveal anything new. Certainly it causes us to question the value of needlessly utilizing hundreds of animals in this type of testing.

Rhodia Inc. also believes the proposed hypersensitivity testing is unwarranted, and that the information provided in the aforementioned review of toxicological literature dated January 2002 to support such testing is inaccurate and misleading.

In Section 9.9 ("Immunotoxicity"), on page 16 of the review of toxicological literature, it states "A delayed-type hypersensitivity response was observed in the mouse ear swelling test (female BALB/c mice were sensitized on the back with 4% sodium metasilicate and then challenged on the ear with 6% sodium metasilicate). Negative results occurred in the murine local lymph node assay (NTP, 2000; cited by CIR, 2001)."

First, there is no structural basis for thinking that sodium metasilicate is capable of either triggering an allergic response itself or forming a hapten and then triggering a response. There are, quite simply, no reactive groups on this inorganic salt. Further, there are reasons to question the validity of the mouse ear swelling test (MEST) cited.

The MEST uses the traditional principle of induction dosing, then challenging with a measure of biological response (ear thickness rather than skin redness, which is used in the traditional guinea pig methods). The MEST has known formulation issues, with the maximum non-irritant concentration being important for the challenge. This is because it has been well-established that irritants can cause the mouse ear to swell, causing false positive results. Typically in the MEST, the induction concentration is allowed to be slightly irritating, but the challenge concentration must not be irritating at all. Thus, it is not uncommon to see induction concentrations that are higher than the concentration used at challenge. In the study cited to support the notion that sodium metasilicate might have allergenic potential, the challenge concentration was actually *higher* than the induction concentration. This causes one to question the validity of the conclusion that sensitization was observed, as opposed to merely irritation-related swelling. In addition, false positives can be observed if the compound residue makes a stable layer on the ear, thus increasing ear thickness. Thus, there is ample reason to believe that this study may have been flawed, both in design and conduct.

By contrast, the murine local lymph node assay (LLNA) is inherently a much better assay for a chemical such as sodium metasilicate, and the results of the LLNA with sodium metasilicate, as cited in the aforementioned review of toxicological literature were negative.

In Section 10.1 ("Sodium Silicate") on page 18 of the review of toxicological literature, it was reported that "A 57-year old man who had come in contact with sodium silicate in a dyeing process experienced recurrent ulcerative lesions on his left hand for two years, as well as contact urticaria. Positive patch tests and a scratch test pointed to sodium silicate as the culprit (Tanaka et al, 1982)" Rhodia Inc. assumes this is another basis for reaching the conclusion that sensitization testing is warranted on sodium metasilicate. The author of the toxicological review may not have realized that contact urticaria results from mechanical pressure on the skin and is *not* an example of allergic sensitization. Many substances that do not cause allergic sensitization can cause contact urticaria. It is, quite simply, a completely different mechanism and phenomenon.

Thus, the only remaining basis for concluding that sodium metasilicate might have some potential to cause allergic sensitization comes from a reference to sodium carbonate causing sensitization and, by inferring structure-activity relationships, that there should be concern for sodium metasilicate. In pursuing this hypothesis, we performed literature searches on Medline and Toxnet found only one relevant reference. That reference clearly states that no sensitization was found in a human study of trona (sodium carbonate) workers. Perhaps, if this study was picked up on a search and the abstract or full reference was not carefully read, it might have been mistaken as a report of sensitization. We can find no evidence that sodium carbonate is a sensitizer, which is also not surprising.

Again, Rhodia Inc. appreciates the opportunity to comment on the nomination of sodium metasilicate for proposed testing, and, for the reasons stated above, believes that both categories of testing being proposed are unnecessary.

Sincerely yours,

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