----- Forwarded by Kevin H Dr Reinert/NAR/RohmHaas on 05/25/2004 03:11 PM -----

Kevin H Dr Reinert

12/01/2003 01:09 PM

To:
cc:
bcc:
Subject: update on resorcinol

In the original Resorcinol work we used the 28-day repeat oral rat with a LOEL of **504 mg/kg**. We used a 1000 X safety factor (10 - intraspecies, 10 - interspecies, and 10 off a 28 day LOEL). This resulted in a Oral Reference Dose of **0.5 mg/kg**.

In the new 2G drinking water study (rats) from the Resorcinol Task Force, they established a NOEL (for full thyroid histo and neural function) of 360 mg/l (**about 45 mg/kg**). This was the highest dose tested.

In a latter two week+ study in preparation for another 2G study, a LOEL of 720 mg/l (**about 90 mg/kg**) was offered.

Since the new 2G study has a 45 mg/kg NOEL and it is the highest dose tested, I think a safety factor of 100 would be the most appropriate, even conservative. This would result in a Oral Reference dose of **0.45 mg /kg**.

The bottom line is that these numbers are essentially the same and I think the 0.5 mg/kg reference dose is still appropriate.

==========

Resorcinol

Human health:

Various in vitro studies carried out between 1985 and 1995 indicate that resorcinol may induce alterations in the thyroid due to inhibition of peroxidase enzymes. In porcine thyroid gland slices, the uptake of iodine to form precursors of mono- and di-iodotyrosine was significantly inhibited. In another experiment porcine thyroid peroxidase was inhibited in the presence of resorcinol at concentrations around 0.3 µg/L. Similarly, resorcinol inhibited lactoperoxidase activity (which is closely related to peroxidase) but at a much more higher concentration (0.22 mg/L). In vitro studies with resorcinol did not show oestrogenic or antioestrogenic activities.

Old non-GLP in vivo studies (1985) had revealed reversible anti-thyroid activity. Recent NTP studies in rats and mice receiving up to 520 (rats) or 420 (mice) mg/kg bw/day by oral gavage in water for 13 weeks did not confirm these data. In these NTP studies changes in adrenal weight have been reported. Given the fact that there was an increase adenal weight in rats, a decrease in mice, no dose-effect relationship, positive at all doses tested, the biological significance of these findings is unclear.

As there are no data available regarding potential effects of

resorcinol on reproduction and fertility, a Resorcinol Task Force is currently performing a study in the rat to examine the potential effects on the postnatal development of offspring. The CSTEE agrees with the report that this is a critical area of uncertainty, as is the adrenal toxicity observed in the NTP studies.

Environment:

The question of potential adverse effects of resorcinol on the reproduction and development cannot be answered given the absence of key data, especially for aquatic organisms which seems to be the only compartment of relevance when considering exposure of wildlife to resorcinol. This uncertainty is planned to be addressed by the Resorcinol Task Force.
The available data on the trout and zebrafish embryos show teratogenic effects at concentrations > 100 mg/L. These studies were conducted by exposing newly fertilized eggs to resorcinol for periods of 60 (trout) or 7 (zebrafish) days, the test solutions were renewed 3 times a week, but no analytical confirmation of the concentrations was performed which slightly impairs the validity of the study. There are discrepancies in the report regarding the available information on the stability of resorcinol in solution in water (table 3.1 p. 3.2 indicates that data on the stability in water are available, whereas in table 10.1 p.10.5 it is written that there is no data on the abiotic aquatic degradation, and on the top of p. 10-41, that "resorcinol
undergoes rapid degradation in water", and finally, the report words (p. 10.28) on the reliability of the acute toxicity tests which are conducted for 24, 48 or 96 hours are : " a number of these studies used a static exposure regime and did not measure the actual test concentrations which raises issues regarding the validity of the data". This point needs clarification. In addition, there is no indication as to whether the effect is endocrine mediated or not.

Conclusion:

The CSTEE agrees with the conclusions of the report that further testing of resorcinol for potential endocrine disrupting effects is needed. This concerns both human health and the environment, issues addressed in the Resorcinol Task Group.

Italy raised some questions regarding Resorcinol and its potential testing in amphibians, and whether it will be possible to observe an effect depending on the different degree of purity of the components used. Dr. Johnson commented that consideration is being given to the need and availability of a suitable test for assessing potential thyroid effects in the amphibians group. In addition, it is expected that due to the potential effects of resorcinol it will be more relevant to focus on invertebrates. Regarding the second question, Dr, Johnson said that different responses to resorcinol, have been observed in mammals (e.g. rats are more susceptible) but the relevance of these results for humans are not known. Dr. Johnson emphasized that the available data for resorcinol is old and Ms. Roncancio invited CALEB to briefly report on the developments of the "Resorcinol Task Force".

CALEB informed that the objective of the “Resorcinol task force” is to fill data gaps. One study in Daphnia magna has been finalised in August and the final report will be available next month. Preliminary results shown that there are no effects on the adrenals glands and/or at the thyroid level, at concentrations 10 times higher than those found normally in the drinking water. The second study is a multigeneration mammalian reproduction study, which involves exposure through drinking water and it is expected to be concluded in 2004, the final report will be available at the end of 2004 / early 2005. Regarding the potential testing in amphibians, the question will be analyzed by the Task Force

GR required clarification on the existence of information regarding neurodevelopmental disorders, due to the potential effect of resorcinol on the thyroid in the foetus development. CALEB informed that on the tests performed, non adverse effects have been observed on the behavioural tests conducted.

Opinions are mine and not those of the Rohm and Haas Company

–