July 7, 2009
Mark W. Townsend, Chief
HPV Chemicals Branch
USEPA Headquarters
Ariel Rios Building
1200 Pennsylvania Avenue, N. W.
Mail Code: 7403M
Washington, DC 20460

Dear Mr. Townsend:

I received your comments on the robust summaries and the test plan for 2-amino-2-hydroxymethyl-1,3-propandiol (THAM). We have updated both the Test Plan and the robust summaries on the IUCLID 4 document and have provided both as attachments. We have made the changes requested by EPA; however, we have also deleted references to the reproductive/developmental endpoints on 2-amino-2-methyl-propanol (AMP). This was done because we have considered the reproductive/developmental properties on THAM and the surrogates used to cover some of the endpoints. We have concluded that AMP has unique reproductive/developmental effects and is not a proper surrogate for this endpoint. This is based on several observations.

First, we are now aware of a reproductive/developmental study on a compound similar to THAM, 1-amino-2-ethyl-1,3-propanediol (AEPD) (see below). In an OECD 422 study conducted in Japan, rats were administered 0, 250, 500 and 1000 mg of AEPD/kg via oral gavage. There were no treatment related effects observed on length of estrous cycle, number of days until copulation, copulation index, insemination index, or fertilization index. Furthermore, there were no effects of test article administration on the gestation period, birth index, numbers of corpora lutea, numbers of implantations, implantation index, parturition or nursing behavior, numbers of stillborn pups, still birth index, numbers of liveborn pups, liveborn index, sex ratio, observation of liveborn pups at birth or necropsy at 4 days postpartum, as well as body weights or viability[1].

Therefore, although there are some similarities of structure between the various amino alcohols that can be utilized for some endpoints, it is apparent that slight alterations of the molecule have profound consequences on the developmental/reproductive characteristics of the chemical and that AMP does not represent a true surrogate for THAM reproductive/developmental toxicity.

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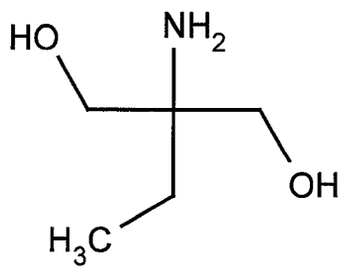
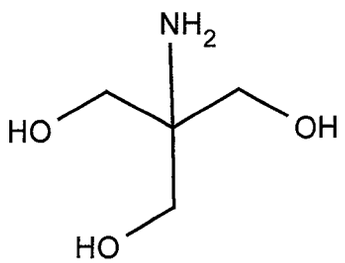
[1] http://dra4.nihs.go.jp/mhlw_data/home/file/file115-70-8.html; Bozo Research Center Inc., 1285 Kamado, Gotemba-shi, Shizoaka, 412-0039, Japan. Tel & Fax +81-550-82-9922.



2-amino-2-ethyl-1,3-propanediol (AEPD)



2-amino-2-(hydroxymethyl)-1,3-Propanediol (THAM)

Secondly, Dow still maintains and EPA agrees that THAM has had a long history of use in various pharmaceutical products without any alleged reproductive and developmental effects. Please be advised that within the last few weeks, we have received FDA's study data on THAM. None of the studies located included reproductive/developmental endpoints as far as we could tell from 'best possible' copies of these reports.

Please also note that on your High Production Volume Information System (HPVIS) website (www.epa.gov/chemrtk/hpvis/index.html), we noticed that under Reproductive Toxicity for THAM (CAS=77-86-1), EPA has listed as the test substance 1,3-Propanediol, 2-amino-2-(hydroxymethyl)-. However, the test substance was actually AMP or 2-Amino-2-methyl-1-propanol (CAS=124-68-5) as noted in the Developmental Toxicity/ Teratogenicity section. Although AMP may not be an appropriate surrogate for this endpoint, this is in error and needs to be corrected.

Dow considers that AMP has unique reproductive/developmental properties. At EPA's discretion we are willing to conduct an OECD 421 study if necessary on THAM. Furthermore, a reproductive/developmental study may also be needed to fulfill requirements for European regulatory purposes under REACH. We suggest that we wait so that the needs of EPA and ECHA can be met. If an OECD 421/422 is needed, its completion would be done before submission in 2013. Should you want to discuss this further, please contact me at (517) 636-9870 or via E-mail at bhughes2@dow.com.

Sincerely,

Brian J. Hughes, PhD, DABT
Toxicologist
The Dow Chemical Corporation