JuanB Perez/DC/USEPA/US
11/16/2006 08:25 AM

To NCIC HPV@EPA
cc
bcc
Subject Fw: HPV submission

----- Forwarded by JuanB Perez/DC/USEPA/US on 11/16/2006 08:25 AM -----

"Stafford, Fran (FM)" <FMStafford@dow.com>
11/15/2006 05:48 PM

To NCIC OPPT@EPA, Rtk Chem@EPA
cc "Cosse, Pam (P)" <PCosse@dow.com>, "Deford, Connie (CL)" <CLDeford@dow.com>, "Stott, William (WT)" <WStott@dow.com>
Subject HPV submission

Attached please find the HPV submission test plan and dossier for Tris(hydroxymethyl)aminomethane (77-86-1). A hard copy and CD were sent via Fed Ex yesterday, (Tuesday, 14 November) with an arrival to EPA by the morning of today, Wednesday, 15 November. However, according to Fed Ex there were weather conditions and a missed courier pick up which did not allow for a Wednesday delivery of the test plan and dossier to EPA. We were not informed that Fed Ex did not deliver the package until after 5:00 pm today (Wednesday, 15 November). We apologize for this unforeseen delay of FedEx not being able to do the next day delivery . We made every attempt to make the November 15th submission day. If you have any questions please contact Pam Cosse 989-638-9660 or Dr. William Stott 989-636-8203.
<<Dossier Tris(hydroxymethyl)aminomethane CAS# 77-86-1.rtf>>
<<Test Plan Tris(hydroxymethyl)aminomethane CAS# 77-86-1.doc>>
Thank you.

Pamela F. Cosse
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Dossier Tris(hydroxymethyl)aminomethane CAS# 77-86-1.rtf Test Plan Tris(hydroxymethyl)aminomethane CAS# 77-86-1.doc

AMINO ALCOHOL

HPV Challenge Program

TEST PLAN
For
Tris(hydroxymethyl)aminomethane (77-86-1)

Submitted to the U.S. Environmental Protection Agency
Under the High Production Volume (HPV) Chemicals Challenge Program

By

The Dow Chemical Company
Midland, Michigan, 48674

November 14, 2006

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I. INTRODUCTION

The Dow Chemical Company has committed to sponsor TRIS AMINO in the EPA High Production Volume Chemical Program.

II. IDENTIFICATION OF THE SUBSTANCE

For more than 50 years, Tris(hydroxymethyl)aminomethane (TRIS AMINO) CAS# 77-86-1, technically described as 2-Amino-2 (Hydroxymethyl)-1,3-Propanediol, has been used in applications ranging from pharmaceuticals, biological buffers, and transport of live aquatic species, to emulsifying agents in cosmetics. TRIS AMINO is widely known and used as a therapeutic biological buffer, predominantly in patients suffering a decrease in blood pH due to diabetes or a wide array of respiratory diseases and conditions. It is also used clinically as a drug for the treatment of metabolic acidosis where it is injected intravenously or via other routes. It is listed in both the U.S. Pharmacopeia and the National Formulary of drugs for therapeutic drug applications. TRIS AMINO is administered in human patients primarily via the intravenous route regardless of the cause of the acidosis. It has been rigorously evaluated in numerous clinical experiments with animals and humans, and has consistently shown a low incidence of long-term toxicological effects at effective doses with relatively few and minor side-effects. TRIS AMINO is also used in the anti-inflammatory Keterolac® to improve drug solubility. In this form, it has been approved for use in treating acute post-operative pain via an intramuscular injection. Keterolac® has been widely used due to its outstanding pain control properties, and is a nondependency-forming alternative to opiates with a low occurrence of side-effects. TRIS AMINO is also listed in the CTFA International Cosmetic Ingredient Dictionary (page 628, entry name of Tromethamine), reflecting its use as an ingredient in various cosmetic formulations.

Because of its low aquatic toxicity, TRIS AMINO is also an effective buffer used to regulate the pH of the water during the transport of live aquatic species. TRIS AMINO is also widely used as a buffer, solubilizer and neutralizing agent in cosmetic creams, solutions, and lotions, mineral oil and paraffin wax emulsions, polishes and cleaning compounds. Finally, TRIS AMINO is also often used as a buffer in various biological test systems and life science applications such as cell culture media.

III. JUSTIFICATION FOR THE USE OF SURROGATE SUBSTANCES TO SUPPORT THE SUBMISSION FOR TRIS AMINO

Table 1: Identification of the surrogate substances

CAS No.	*Chemical Acronym*	Chemical Name
000077-86-1	TRIS AMINO, THAM, TA, TRIS, TROMETHAMINE	Tris (hydroxymethyl) aminomethane (2-Amino-2-hydroxymethyl-1,3-propanediol)
000115-69-5	AMPD	2-Amino-2-methyl-1,3-propanediol
000124-68-5	AMP, AMP-95	2-Amino-2-methyl-1-propanol

A common mechanism of action, based on structural and chemical similarity, is one of the bases that the EPA has provided under the HPV program to use structurally-similar substances as data surrogates (U.S. EPA, 1999). We propose to utilize surrogate chemicals to fill gaps in our HPV data base for TRIS AMINO.

TRIS AMINO (2-Amino-2-hydroxymethylpropanediol) and the proposed surrogate compounds 2-Amino-2-methyl-1,3-propanediol (AMPD) and 2-Amino-2-methyl-1-propanol (AMP) possess an identical molecular "backbone" structure and common functional groups, forming a continuum from triol to diol to mono-alcohol, respectively. These structures are shown in Figure 1. TRIS AMINO, AMPD and AMP all contain a primary amine connected to a tertiary carbon, with one or more terminal primary alcohol groups

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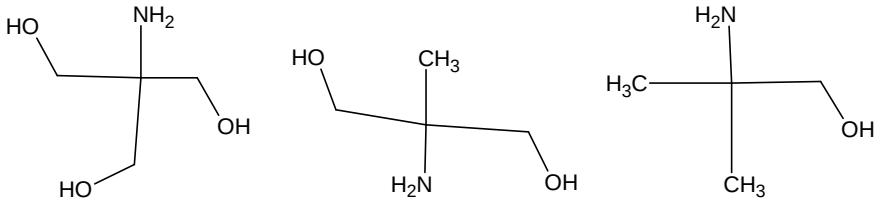
Figure 1. Representative Structures of the Surrogate Substance(s)



TRIS AMINO AMPD AMP

Table 2: Chemical Properties of TRIS AMINO and of the Surrogate Substances

Test Chemical	CAS No.	Molecular Wt. g/mol	Melting Point	Boiling Point	Vapor Pressure	Partition Coefficient	Water Solubility

			(°C)	(°C)	(hPa)	Log K_{ow}	(g/L)
TRIS AMINO	77-86-1	121.14	171-172	219-220 @ 10 mm Hg	$3.04x10^{-6}$	-2.31	800
AMPD	115-69-5	105.14	110	151-152 @ 10 mm Hg	$8.71x10^{-3}$	<-3.8	2500
AMP	124-68-5	89.14	30.5	165.5 @ 760 mm Hg	$4.5.3x10^{-1}$	-0.63	Miscible all proportions

Consistent with the general structural and chemical similarities of TRIS AMINO, AMPD and AMP, studies have demonstrated a similar pattern of physical chemistry, environmental fate, and ecological and mammalian toxicity profiles. The compounds are solid crystalline masses in the pure or neat state, and possess common general physical/chemical properties. Because of their structure, all the substances are highly soluble in water, have very low vapor pressures, possess relatively low partition coefficients (log K_{ow}'s), and similar dissociation constants, making them likely to remain dissolved in the water compartment upon the event of an environmental release, where biodegradation is ultimately expected. MacKay Level III fugacity modeling predicts that TRIS AMINO and the surrogate substances will tend to partition predominately to water Gonsior (2006). There is also a low potential to bioaccumulate in aquatic organisms based on low log K_{ow} values. The high water solubility and negligible vapor pressure of all three substances support the low estimated Henry's Law Constants ($4.54x10^{-8}$ and $6.48x10^{-10}$ Pa m^3/mol for TRIS AMINO and AMP, respectively, and 8.67 $x10^{-13}$atm-m^3/mole for AMPD).

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The data on fish, aquatic invertebrate, and algal toxicity, in addition to the use of TRIS AMINO as a buffer for live fish transport, indicate a pattern of low toxicity for this chemical and the surrogate substances. These materials are of low toxicity to aquatic organisms with EC50s greater than 100 mg/L.

Mammalian toxicity studies have displayed similar results. The oral LD_{50} value for TRIS AMINO is 5500 mg/kg in the mouse, and its surrogates range from 2150 to greater than

5000 mg/kg in the rat and mouse. TRIS AMINO was non-irritating to eyes when a 40% aqueous solution was applied to the eyes of rabbits (pH 10.4 for 0.1M aqueous solution). In contrast, 95% AMP in water was severely irritating to the eyes, presumably due to the severely alkaline pH of the test solution used (pH 11.3 for 0.1M aqueous solution); however, more neutral cosmetic formulations containing lower concentrations of AMP are only minimally irritating. There is no sensitization data available for TRIS AMINO; however, based on the following data, TRIS AMINO is not expected to be a sensitizer. Laboratory animal test samples of AMP did not cause allergic skin reactions when tested in guinea pigs following topical or intradermal administration. In patch tests with humans, AMP and cosmetic formulations containing either AMP or AMPD were negative for dermal sensitization.

Repeated-dose mammalian toxicity studies conducted on TRIS AMINO and the two surrogate chemicals indicate that the compounds are generally well-tolerated at concentrations as high as 500 mg/kg/day via IV infusion for TRIS AMINO and ingestion of up to 3200 ppm in the rodent diet (250-750 mg/kg/day for rats and mice, estimated). A number of human clinical trials of the IV infusion of TRIS AMINO have also been successfully conducted. In all studies, the only target tissue, when observed at all, has been the liver with AMP. Human clinical studies with Keterolac® (a major component of which is TRIS AMINO) have suggested that patients with decreased liver function not be given the drug over extended treatment periods based upon changes in several clinical chemistry parameters. Ingestion of relatively high dosages of AMP has caused liver histopathological changes in rats and dogs. The most significant toxicological activity has been a fetotoxic effect of AMP when ingested at relatively high levels by pregnant rats. Subsequent dermal exposure to comparable dosages failed to elicit a developmental effect in rats. Overall, there have been no consistently-noted observations or treatment-related findings among the numerous repeated-dose mammalian toxicity studies that have been conducted over the last 50 years on these compounds that would indicate long-term significant toxicity of either compound at typical human exposure levels. Reflective of these findings is the fact that both TRIS AMINO and AMP display similar patterns of excretion from the body, being primarily eliminated unchanged via the urine over a relatively short period of time. Further, no evidence of either direct reactivity or metabolism to reactive species toward genetic

material has been observed. Genetic toxicity studies conducted on the TRIS AMINO and the surrogate substances in the presence or absence of mammalian metabolic enzymes have all been negative.

Finally, TRIS AMINO and the surrogate chemicals have displayed little if any toxicity to humans during their long history of use as human drugs and/or in personal care products and cosmetics. TRIS AMINO has found use as an IV drug for the management of acidosis in humans for many years and the toxicity of AMPD and AMP have been reviewed by the Cosmetic Ingredient Review Expert Panel which concluded that these materials are safe as used in cosmetic formulations up to 1% (CIR, 1990).

Comment [PFC1]: *Pam does this reference include AMPD?*

Based upon the properties, uses and toxicities of TRIS AMINO, AMPD and AMP, the use of AMPD and AMP as surrogate substances to fulfill any data gaps for TRIS AMINO is warranted.

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IV. DEVELOPMENT OF ROBUST SUMMARIES AND STUDY SCORING CRITERIA

The Dow Chemical Company has chosen to use the IUCLID (International Uniform ChemicaL Information Database) format for preparation of robust summaries for the HPV program. Because many of the fields in the IUCLID database program are outside the scope of the HPV program, these fields are typically left blank in the IUCLID robust summary. Scoring of studies from company files or from the literature for reliability to fulfill the testing requirement for each endpoint used a system similar to that published by Klimisch *et al*. (1997). Studies were given a score of "1" if the data could be considered valid without restriction based on the completeness of the protocol and adequate details in reporting. Studies were given a score of "2" if the data and study design could be considered scientifically valid to address the endpoint but with restrictions due to lack of various technical or reporting details or deviations from current OECD guidelines. Studies were given a score of "3" if their conduct was not acceptable and "4" if there wasn't enough information present to assign a reliability rating. However, a study receiving a score of "4" could provide supplementary information that could be used to address the endpoint in a weight of evidence evaluation in the absence of other data.

V. TEST ENDPOINT RESULTS FOR TRIS AMINO and SURROGATE SUBSTANCES

A summary of the data on HPV/SIDS endpoints for TRIS AMINO and structurally similar amino alcohols can be found in **Table 3: Summary of the Endpoints**.

Evaluation of this data leads to the conclusions that (1) a substantial quantity of data currently exist to adequately represent the toxicological and ecological profile, (2) there is concurrence and similarity among the existing data for the various HPV/SIDS endpoints, (3) available data from TRIS and the structurally similar substances can be used to adequately represent the various HPV/SIDS endpoints that may not have been subjected to the same level of testing, and (4) utilization of these data support the conclusion that no further testing is needed for most of the HPV/SIDS categories. The data for each of the HPV/SIDS endpoints are discussed in the following section.

A. Melting Point

IUCLID 2.1: TRIS AMINO is crystalline masses in the neat or pure state with melting points of 171-172^{o}C (Merck, 1989). The data suggest that decomposition is unlikely, and because the melting point is well-documented in peer-reviewed literature and public databases, **further testing for this endpoint would not be productive**.

B. Boiling Point

IUCLID 2.2: The boiling point for TRIS AMINO is well documented (Merck, 1989). **No further testing is planned for this endpoint.**

C. Vapor Pressure

IUCLID 2.4: The vapor pressure for TRIS AMINO was estimated by EPIWIN MPBPWIN program, and although estimations are not considered reliable for this category, both the experimental or estimated values for the structurally similar amino alcohols are extremely low at $3.0x10^{-6}$ (TRIS AMINO) hPa at 20-25^{o}C. The vapor pressure, for the structurally related substances have been well-documented in either measured reports, published literature or chemical handbooks. This result is consistent with the physical/chemical nature of the amino alcohols and suggests a very low degree of volatility; there is **no further testing planned for this endpoint**.

D. Partition Coefficient

IUCLID 2.5: The value for TRIS AMINO is –2.31(Lhotak, 1996). The partition coefficient is consistent with high water solubility and which by definition would be

indicative of low log K_{ow} values. Based on the structure, and the low log K_{ow} values, **no further testing of this endpoint is necessary.**

E. Water Solubility

IUCLID 2.6.1: Measured data indicate that TRIS AMINO is highly soluble to miscible in water. Measured aqueous solubilities of at least 800 g/l at 25 ^{o}C for TRIS AMINO further document its very high water solubility (L. Troester, personal communication, 2006). Furthermore, TRIS AMINO is sold as an aqueous solution, and is formulated as part of the drug Keterolac® to enhance its solubility. Sufficient data exist for this endpoint to characterize water solubility for the TRIS AMINO, such that **no further testing is needed**.

F. Photodegradation

IUCLID 3.1.1: TRIS AMINO does not absorb light >290 nm, and therefore direct photolysis is not possible. Indirect photolysis (hydroxyl radicals) is possible, however. Modeling has shown that the half-life of TRIS AMINO in the atmosphere is approximately 3.8 hours (West, 2004a). Since volatilization is not an important environmental fate process for the surrogate substances, testing for photolysis in the atmosphere is not relevant, and therefore **no further testing for this endpoint is necessary**.

G. Stability in Water (Hydrolysis)

IUCLID 3.1.2: TRIS AMINO does not possess molecular structures that contain functional groups subject to hydrolysis under neutral ambient conditions (Reaction Mechanisms in Environmental Organic Chemistry, 1994). It is commercially available as an aqueous mixture, further documenting high stability in water, and is reported stable for several years <200^{o}C. This testing endpoint is well characterized, and **no additional testing is required.**

H. Environmental Transport

IUCLID 3.3.1: Environmental transport data were obtained for the TRIS AMINO by estimation using the EPIWIN Level III Fugacity program (Canadian Environmental

Modeling Center). Measured water solubility data and the previously-reported values for vapor pressure were used as the model input. The program also used input values for octanol/water partition coefficients, air-water coefficients, melting point and molecular weight that were either calculated by other programs in the EPIWIN suite or used as reported in peer-reviewed literature or databases.

The fugacity mass amount (partitioning) values obtained indicate that distribution into the air would be negligible (<0.1%), as would be expected for primary amino alcohols compounds with low volatility and high solubility in water. Likewise, the distribution to sediment was estimated to be <0.1%. The calculated mass amounts in the soil environmental compartment was <0.1%; the predicted mass amounts distributed to water was 100.0%, a high level that is consistent with the known high water solubility of members of this category (Gonsior, 2006).

Although the values obtained using this model should not be regarded as quantitative, the model results are consistent with the known physical and chemical properties of TRIS AMINO, i.e., the known high water solubility and negligible volatility. **Further testing for this endpoint is not needed.**

I. Biodegradation

IUCLID 3.5: Biodegradation is the conversion of a chemical by microorganisms in the environment into its simpler components and ultimately to carbon dioxide and its other constituent molecules. Chemicals are classified as readily biodegradable by the Organization for Economic Development (OECD) guidelines if there is a 70% degradation of dissolved organic carbon within a 10-day period during a typical 28-day laboratory protocol.

There is a biodegradation study, OECD 301D, for TRIS AMINO which indicates that it is not readily biodegradable (IWL, 1990). There is evidence based on studies with structurally-related compounds to suggest that TRIS AMINO would biodegrade under favorable conditions. There is an OECD 302C study on AMPD which showed 96.7% biodegradation after 22 days. It should therefore be considered inherently biodegradable, which indicates that it would not persist indefinitely in the environment

and that it would exhibit similar biodegradation potential based on structure-biodegradability relationships measured for similar compounds (West, 2004b).

These data indicate that there is sufficient information on the biodegradation potential of TRIS AMINO and of the surrogate substances, and justifies that **no additional testing is needed.**

J. Acute Fish Toxicity

IUCLID 4.1: The LC_{50} value of TRIS AMINO for 29 species of fish was reported to be greater than 4400 mg/L when observed for a period of 30 days; it is used as a buffering agent for shipping live fish at dose levels ranging 440-1100 mg/L under aerated or static conditions (McFarland and Norris, 1958). AMP has been evaluated in 96-hour LC_{50} testing with *Lepomis macrochirus*, where the LC_{50} under semi-static conditions was reported to be approximately 190 mg/L (Parekh, 1980a). **No additional testing is required.**

K. Aquatic Invertebrates

IUCLID 4.2: Based on toxicity trends in fish, and comparable physical-chemical properties, TRIS AMINO is expected to be as non-toxic to aquatic invertebrates as AMP. Aquatic invertebrate toxicity data are available for AMP only, and the authors report 48- & 96-hour LC_{50} values for *Crangon crangon* to be 179 mg/L (Young and Tapp, 1983). In *Daphnia magna*, AMP was reported with a 48-hour EC_{50} of 193 mg/L (Parekh, 1980b). **No additional testing is required**.

L. Aquatic Plants

IUCLID 4.3: TRIS AMINO was tested with *Selenastrum Capricornutum*, and a NOEC of >100 mg/L in a 96-hour growth rate test (Adams, *et al*., 1985). **No additional testing is considered necessary.**

M. Acute Oral Toxicity

IUCLID 5.1.1: Acute oral toxicity studies were conducted with TRIS AMINO using a gastric tube in the Swiss mouse and Wistar rat. Solutions of 20% and 5% were given via the gastric tube to rats and mice respectively at doses of 1000, 2000, and 3000

mg/kg as a solution. The LD_{50} for rats and mice are estimated to be >3000 mg/kg in solution. There was no toxicity noted in either species at the top dose levels, although abundant urine output was noted for some animals (Giroux and Beaulaton, 1962). **Additional testing is not considered necessary**.

N. Acute Inhalation Toxicity

IUCLID 5.1.2: There is no available data on TRIS AMINO or the surrogate substances for this endpoint. There is, however, a low potential for inhalation exposure based on known use patterns, physical state of the pure materials, and vapor pressure, and **therefore testing is considered unnecessary**.

O. Acute Dermal Toxicity

IUCLID 5.1.3: TRIS AMINO has been evaluated in the rat and mouse via intradermal injections, and the LD_{50} for both species exceeded 1000 mg/kg body weight, the highest dose tested. At that dose level, lesions were noted, but no other signs of toxicity were reported (Giroux and Beaulaton, 1962). AMP was evaluated in rabbits via a 24-hour skin patch test, and the LD_{50} was reported greater than 2000 mg/kg (Parekh, 1980c). There were no signs of systemic toxicity, however the treatment sites were necrotic within 2-3 days, and remained so at study termination. Treated groups exhibited a loss in body weight over the 14-day post-treatment period.

No additional testing for this endpoint is considered necessary, as reliable data is available for TRIS AMINO and the surrogate compound AMP.

P. Skin Irritation

IUCLID 5.2.1: Skin irritation tests following the Draize Method have been performed on TRIS AMINO, although documentation is not sufficient for full assessment (reliability 4). It was found to be moderately irritating on abraded rabbit skin, but resolved within 48 hours (Baldwin, 1961). There was no noticeable irritation on unabraded skin sites. In a more reliable study, AMP was found to be irritating to rabbits, with burrowing lesions noted when applied to abraded skin sites (Machle *et al*., 1940); there was mild irritation noted when applied to unabraded skin. The severity of irritation is directly related to the base strength of the amino alcohol. At 25°C the pKa

of TRIS AMINO is 8.03, the pKa of AMPD is 8.76, and the pKa of AMP is 9.72. Since limited data exists for the compound, but exists for the surrogate substances, **additional testing is not considered necessary**.

Q. Eye Irritation

IUCLID 5.2.2: Undiluted TRIS AMINO was found to be essentially non-irritating to rabbits, although documentation is not sufficient for full assessment (reliability 4). Another test conducted on a 40% solution of TRIS AMINO in water has shown this material to be non-irritating to rabbits (Power, 1975). **No additional testing is necessary.**

R. Skin Sensitization

IUCLID 5.3: While the toxicological/safety profile of TRIS AMINO has been extensively established for many endpoints, especially those associated with its use in the treatment of metabolic acidosis, no laboratory studies of skin sensitization have been reported for this material, and the assessment for dermal sensitization has been based on the favorable use experience associated with various uses, such as applications where it is an ingredient in formulations associated with anticipated dermal contact. In addition, structurally related surrogates AMPD and AMP have been negative in laboratory animal and/or human patch tests for sensitization. AMP did not cause allergic skin reactions when tested in guinea pigs following topical or intradermal administration. In patch tests with humans, cosmetic formulations containing either 0.22% AMP or 0.5% AMPD or 0.075% AMPD were negative for dermal sensitization (Kociba, 2003; CIR, 1990). **Based upon extensive clinical use and surrogate related chemical activities no further testing is recommended.**

S. Repeated-Dose Toxicity

IUCLID 5.4: TRIS AMINO was administered to various species of animals and humans in multiple studies and trials primarily via the intravenous route, since it is delivered in that manner to human patients suffering acidosis and requiring treatment. The test durations ranged from 10 to 99 days in rats, mice, and rabbits. In all studies, regardless of duration or species, the observations consistently noted were lesions and / or gangrene at the infusion sites, and, in many cases, increases in white blood cell

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counts associated with gangrene. Sporadic kidney and liver lesions were noted in the longer studies. Because the studies were generally conducted at one dose level (plus control) comparable to human therapeutic doses, no-observed-adverse effect level (NOAEL's) / lowest-observed-adverse effect level (LOAEL's) are not useful to report. It is reasonable to assume, however, that since the studies were conducted under very likely human exposure scenarios, the relative toxicity of TRIS AMINO to humans is low. The assumption of low toxicity is also supported by multiple clinical trials with both healthy and ailing human patients treated with TRIS AMINO at similar dose levels. In these clinical trials, the most common observations included a transient decrease in respiratory rate, an increase in urine output, hyperkalemia, and hypoglycemia. In cases where the dose level far exceeded the recommended therapeutic dose, vomiting, sweating, hunger, dizziness, and diarrhea occurred in a small subset of the test group. There are no documented long-term effects of TRIS AMINO treatment, and no serious side-effects on record that are directly attributed to treatment with the compound.

The surrogate chemical AMP has been more thoroughly tested in mammalian species via more traditional industrial safety and handling toxicity test than TRIS AMINO. The repeated dose toxicity of AMP has been well-studied and documented. These dietary studies ranged from eight weeks to one year in multiple species. The primary treatment-related effect noted has been histopathological changes consisting of increased liver weights and vacuolation of the liver in rats and dogs (Parekh, 1981; 1981b; Griffin, 1990). **No further testing of TRIS AMINO is recommended.**

T. Genetic Toxicity: Gene Mutations and Chromosome Aberrations

IUCLID 5.5 and 5.6: TRIS AMINO was negative in a gene mutation assay in *Saccromyces cerevisiae*, and negative in the bacterial gene mutation assay with *E.coli* (Livtak and McEvoy, 1990). **No additional testing is considered necessary**.

U. Carcinogenicity

IUCLID 5.7: TRIS AMINO did not induce tumors when tested in male Syrian golden hamsters receiving 0.2 ml of a mixture of Tris buffer and 0.9% NaCl intratracheally into the lungs weekly for life (Ketkar, M. *et al*., 1979). The long history of safe use of TRIS

AMINO as a biological buffer in the treatment of acidosis, its use in Keterolac®, an anti-inflammatory drug, and the compound's use in cosmetics over many years suggest that TRIS is not carcinogenic. Repeated dose toxicity studies of TRIS and the structurally related primary amino alcohol, AMP, do not show any evidence of any preneoplastic lesions, and mutagenicity studies are all negative; a one-year study of AMP in dogs (Griffin, 1990), indicated no evidence of carcinogenicity. **These data suggest that the materials are not carcinogenic. No additional testing is considered necessary.**

V. Reproductive Toxicity

IUCLID 5.8.1: There have been no reproduction studies conducted with TRIS AMINO. Data are available to indirectly evaluate the potential for reproductive effects from exposure via chronic studies that include histological examination of gonadal tissues for evidence of adverse effects. No adverse clinical, histological, or hematological effects were noted in more than a dozen repeated-dose toxicity studies conducted with AMP and AMPD that would indicate toxicity to the reproductive organs. Likewise, there have been no reports of any reproductive effects in the multiple studies conducted on human patients with TRIS AMINO. However, in a recent rat reproductive/developmental screening study, the HCl salt of AMP has been observed to be fetotoxic in rats. An OECD 421 study was conducted using AMP-HCl in which male and female CD rats were fed diets supplying 0 (control), 100, 300, or 1000 mg/kg/day of AMP-HCl (Carney *et al.*, 2005). Males were exposed for at least two weeks prior to breeding and continuing throughout breeding for 37 days. The females were exposed for two weeks prior to breeding, continuing through breeding (up to two weeks), gestation (three weeks), and lactation (four days). Evidence of complete litter resorption (100% post-implantation loss) was seen at 1000 mg/kg/day, and significant resorptions were seen at 300 mg/kg/day. Effects associated with, or secondary to the post-implantation loss increase at 300 mg/kg/day included decreased litter size, increased pup body weight, and decreased gestation body weight and body weight gain. The no-observed effect level (NOEL) for systemic toxicity in males was 100 mg/kg/day, but could not be established for females due to liver effects in the low dose group; the NOEL for reproductive toxicity was 100 mg/kg/day. There were no treatment related effects on reproductive performance in the 100 mg/kg/day group. The NOEL for general toxicity in males was 300 mg/kg/day, while the general toxicity NOEL for females could not be

determined, based upon the presence of very slight microscopic liver effects. The NOEL for reproductive effects was considered to be 100 mg/kg/day.

In light of the history of TRIS AMINO use in pharmaceuticals and no direct evidence of reproductive toxicity associated with TRIS AMINO, we believe that reproduction/developmental toxicity data may exist. We plan to explore this further by filing a Freedom of Information Act (FOIA) request with the US Food and Drug Administration (FDA) to determine if such testing has been conducted. In the event that we do not obtain this data, then we commit to conducting an OECD 421 reproductive and developmental screening study similar to that conducted on AMP to fully evaluate any potential fetotoxicity of TRIS AMINO in rats.

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W. Developmental Toxicity

IUCLID 5.82: Data are not available for TRIS AMINO. However, an OECD 414 GLP guideline study on AMP is available. In this study, female rats were exposed 6 hours daily dermally to 0, 30, 100, or 300 mg AMP/kg/day from gestation days (GD) 6-20 (Carney and Thorsrud, 2006). Dermal administration of 300 mg/kg/day of AMP produced significant effects at the test site, as evidenced by scabbing and moderate to severe scaling. The dermal finding of slight scaling at 30 and 100 mg/kg/day was not considered adverse, as the observation was transient in nature and relatively low in incidence. There was no evidence of test article related systemic maternal or developmental toxicity at any dose level tested. Under the conditions of this study, the NOAEL for maternal toxicity based on dermal effects was 100 mg/kg/day. The NOEL for developmental toxicity was 300 mg/kg/day, the highest dose level tested. While this study is believed to represent a definitive evaluation of potential developmental toxicity for TRIS AMINO in addition to AMP, it is believed that given the extensive use of TRIS AMINO as a therapeutic agent data exist within US FDA archives to address this endpoint (FOIA reference noted in Reproduction Section and below). Should no data be identified, a proposed OECD 421 reproductive and developmental screening study will provide an additional evaluation of any potential for developmental toxicity TRIS AMINO.

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VI. CONCLUSIONS

Evaluation of the existing data leads to the conclusions that [1] a substantial quantity of data currently exist to adequately represent the toxicological and ecological screening profile of the category, [2] there is a concurrence and similarity among the existing data for the various HPV/SIDS endpoints [3] available data from previously studied structurally similar primary amino alcohols can be used to adequately represent the majority of the various HPV/SIDS endpoints for the compound that was not subjected to the same level of testing (with the exception of acute inhalation and developmental toxicity), and [4] utilization of these data support the conclusion that no further testing is needed to satisfy endpoints for HPV/SIDS with the exception of Reproductive toxicity. (Table 4: Test Plan Matrix). However, TRIS AMINO has a long history of safe use in pharmaceutical products intended for use internally in humans. We believe that reproduction/developmental toxicity data may exist**,** so the FOIA inquiry with the FDA will determine if such testing has been conducted. If no data is found we will then commit to conducting an OECD 421 reproductive and developmental screening study. Further, a proposed OECD 421 reproductive/developmental toxicity screening test will provide data on the potential developmental toxicity of TRIS AMINO.

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Table 3: Summary of the Data

		SURROGATE SUBSTANCES	
	TRIS AMINO (77-86-1)	***AMPD (115-69-5)***	**AMP (124-68-5)**
PHYSICAL CHEMISTRY			
Melting point, °C	*171-172*	*110*	*30.5*
Boiling point, °C	*219-220 °C @ 133.3hPa* *290.9 °C @ 1013hPa*	*151-152*	*165°C @ 1013hPa*
Vapor Pressure @ 20°C	*$3.0x10^{-6}$hPa*	*$8.71x10^{-3}$ hPa*	*$4.5.3x10^{-1}$ hPa*
Water Solubility @ 25°C	*800 g/L*	*2500 g/L*	*Miscible all proportions*
Log K_{ow}	*-2.31*	*<-3.8*	*-0.63*
Estimated LogD (log K_{ow} @ pH 7)	*-2.22*	--	*-2.77*
Density	*0.932 g/cm^3 @ 20°C*	---	*0.928 g/cm^3 @ 20°C*
ENVIRONMENTAL FATE			
Biodegradation	*Not inherently*	*inherently*	*Not inherently; does not biodegrade*
Hydrolysis	*Not expected*	*Not expected*	*Not expected*
Photodegradation	*Direct photolysis not expected.*	*Direct photolysis not expected.*	*Direct photolysis not expected.*
Transport between Environmental Compartments: (**Fugacity Level III Model**) Default assumption: 1000 kg/hr released simultaneously into air, water, and soil.	*<0.1% to air* *68.6% to water* *31.4% to soil* *<0.1% to sediment*	---	*0.07% to air* *73.9% to water* *26.0% to soil* *0.03% to sediment*
ECOTOXICITY			
Acute Toxicity to Fish (LC_{50})	*Non-toxic to 29 species in concentrations up to 4400 mg/L. Used as a buffering agent at 440-1100 mg/L for shipping live fish*	*96-h static LC50 in zebrafish is >10,000 mg/L*	*Marine LC_{50}(96h)= 184 mg/L in Pleuronectes platessa* *Freshwater LC_{50}(48h) = 331mg/L in*

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			Leuciscus idus
Acute Toxicity to Aquatic Invertebrates (48hr LC_{50})	---	---	*LC_{50} = 179 mg/L in Crangon crangon* *EC_{50} = 193 mg/L in Daphnia magna*
Toxicity to Aquatic Plants	*72-hour growth rate NOEC > 200 mg/L; 96-hour growth rate NOEC > 100 mg/L in Selenastrum capricornutum*	---	*72-hour EC_{50} = 520 mg/L in Scenedesmus sp.*
TOXICOLOGICAL DATA			
Acute Toxicity (oral)	*LD_{50} > 3000 mg/kg in rats (20% solution) & mice (5% solution)*	*LD50 was 3500 - 4400 mg/kg in mice* *LDLo=140 mg/kg in mice* *LDLo= 1500 mg/kg in rabbits*	*LD_{50} = 2900 ± 140 mL/kg in rats* *LD_{50} = 2150 mL/kg in mice* *LDlo = 1000-2000 mL/kg in rabbits*
Acute Toxicity (dermal) mg/kg	*LD_{50} > 1000 mg/kg in rats & mice*	---	*LD_{50} > 2000 mg/kg in rabbits*
Acute Toxicity (inhalation)	---	---	---
Acute Toxicity (other routes)	*LD_{50} = 3280-4040 mg/kg in rats via tail vein* *LD_{50} = 6000 mg/kg in rats via tail vein* *LD_{50} = 6100 mg/kg in mice via tail vein*	---	*LC_{50} = 325 mg/kg in mice i.p. dose*
Acute Skin Irritation	*In rabbits, a mild irritant on abraded skin, resolved within 48 hours*	---	*In rabbits, an irritant in abraded (burrowing lesions) or intact (dermatitis) skin.*
Acute Eye Irritation	*In rabbits, saturated TRIS AMINO solution (40%) is essentially non-irritating.*	---	*In rabbits, vision was destroyed if eyes were flushed or unflushed. Neat AMP is highly irritating likely due to high pH.*
Sensitization	---	*0.1% negative on*	*Intracutaneous test*

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		Guinea Pig	*and a later patch test with guinea pigs found AMP to be a non-sensitizer.*
Repeated Dose Toxicity	*NOAEL = 500 mg/kg of 0.3M THAM in Sprague-Dawley rats for 20 days of infusions.* *NOAEL > 0.5mg/kg of 0.3M THAM for 4 weeks via IV in rabbits*	*20-Day dermal rabbit – No effects*	*LOAEL < 25ppm via diet for 12 weeks in Sprague-Dawley rats (increased liver weights)* *LOAEL~1000ppm via diet for 8 weeks in Sprague-Dawley rats (alopecia & focal skin erosions)* *NOAEL > 3200ppm via diet for 8 weeks in CD-1 mice* *NOAEL = 25ppm via diet for 13 weeks in dogs (clin chemistry & organ weight changes suggesting liver as target organ)* *NOAEL > 110ppm via diet for 1 year in dogs*
Genetic Toxicity-Mutation	*Bacterial cell gene mutation assay (bacterial strains)- negative*	*Not mutagenic in 4 strains of Salmonella, with or without metabolic activation*	*AMES Test – negative* *Mammalian cell gene mutation assay – negative* *Bacterial Reverse Mut. Assay – negative*
Genetic Toxicity-Chromosomal Aberrations	---	---	*Mouse Micronucleus Assay- negative*
Toxicity to Reproduction	---	---	*A 1 year dietary dog study revealed no gross or histopathologic effect on testes, uteri, or ovaries (NOAEL > 110ppm)* *NOEL for general*

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			toxicity in male rats was 300 mg/kg/day; the general toxicity NOEL for female rats could not be determined, based upon the presence of very slight microscopic liver effects. NOEL for reproductive effects is 100 mg/kg/day. (OECD 421 study)
Developmental Toxicity	---	---	*NOAEL for maternal toxicity based on dermal effects was 100 mg/kg/day. The NOEL for developmental toxicity was 300 mg/kg/day, the highest dose level tested. (Developmental study in rats OECD 414)*

Table 4: Test Plan Matrix

	TRIS AMINO (77-86-1)	***AMPD (115-69-5)***	**AMP (124-68-5)**
PHYSICAL CHEMISTRY			
Melting point, °C	*171-172 (measured)* *A* No Data	*110 (measured)* No Data	*30.5 (measured)* No Data
Boiling point, °C	*219-220 (measured)* *A* No Data	*151-152 (measured)* No Data	*165 (measured)* No Data
Vapor Pressure @ 20°C	*$3.0x10^{-6}$hPa (calculated)* *Calc* No Data	*$8.714x10^{-3}$ hPa (calculated)* *Calc* No Data	*$4.5.3x10^{-1}$ hPa (calculated)* *Calc* No Data
Water Solubility @ 25°C	*800 g/L (measured)* *A* No Data	*2500 g/L (measured)* *Exp* No Data	*Miscible all proportions (measured)* No Data
Log K_{ow}	*-2.31(measured)* *A* No Data	*<-3.8 (measured)* No Data	*-0.63* *Calc* No Data
ENVIRONMENTAL FATE			
Biodegradation	*Not Inherently(measured)* *A* No Data	*Inherently(measured)* No Data	*Not inherently; does not biodegrade Calc* No Data
Hydrolysis	*Not expected* *NA* No Data	*Not expected* *NA* No Data	*Not expected* *NA* No Data
Photodegradation	*Direct photolysis not expected.* *NA* No Data	*Direct photolysis not expected.* *NA* No Data	*Direct photolysis not expected.* *NA* No Data
Transport between Environmental Compartments: (**Fugacity Level III Model**) Default assumption: 1000 kg/hr released simultaneously into air, water, and soil.	*<0.001% to air* *68.6% to water* *31.4% to soil* *<0.1% to sediment* *Calc* No Data	---	*0.07% to air* *73.9% to water* *26.0% to soil* *0.03% to sediment* *Calc* No Data
ECOTOXICITY			
Acute Toxicity to Fish (LC_{50})	*Non-toxic* *A* No Data	*LC_{50} (96-h) static in zebrafish is >10,000 mg/L*	*LC_{50}(48h) in Bluegill sunfish* Y
Acute Toxicity to Aquatic Invertebrates (48hr LC_{50})	*R*	*R*	*EC_{50} in Daphnia magna* Y

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Toxicity to Aquatic Plants	*72-hour growth rate NOEC in Selenastrum capricornutum* *A* No Data	---	*72-hour EC_{50} in Scenedesmus sp.* No Data
TOXICOLOGICAL DATA			
Acute Toxicity (oral)	*LD_{50} in rats* *A* No Data	*LD_{50} in mice and rats*	*LD_{50} in mice and rats* N
Acute Toxicity (dermal) mg/kg	*LD_{50} in rats & mice* *A* N	---	*LD_{50} in rabbits* N
Acute Toxicity (inhalation)	*NA*	*NA*	*NA*
Acute Skin Irritation	*Irritant* *A* N	---	*Irritant* N
Acute Eye Irritation	*Non-irritating* *A* No Data	---	*Highly irritating likely due to high pH.* N
Sensitization	*Non-sensitizer* *R*	*Non-sensitizer*	*Non-sensitizer* N
Repeated Dose Toxicity	*20-day IV in rats* *4-week IV in rabbits* *R*	---	*Diet (12 weeks) in rats* No Data *Diet (8 weeks) in rats* No Data *Diet (8 weeks)in mice* No Data *Diet (13 weeks) in dogs* No Data *Diet (1 year) in dogs* Y N, Y
Carcinogenicity	*Test Negative for tumors* *A*		*Negative*
Genetic Toxicity-Mutation	*Negative* *A* N	*Negative*	*All negative* Y
Genetic Toxicity-Chromosomal Aberrations	*R*	---	*Negative* Y
Toxicity to Reproduction	*Test (Dependent on FOIA result)*	---	*One year dietary dog study* Y *OECD 421 in rats* Y
Developmental Toxicity	*Test (Dependent on FOIA result)*	---	*OECD 414 in rats* Y

Legend	
Symbol	**Description**
R	Endpoint requirement fulfilled using Structurally related information
Test	Endpoint requirements to be fulfilled with testing
Calc	Endpoint requirement fulfilled based on calculated data
A	Endpoint requirement fulfilled with adequate existing data
Exp	Endpoint requirement fulfilled via experimentation
NR	Not required per the OECD SIDS guidance
NA	Not applicable due to physical/chemical properties
Y	Yes (GLP)
N	No (GLP)
No Data	No data on GLP status

IUCLID

Data Set

Existing Chemical	:	ID: 77-86-1
CAS No.	:	77-86-1
Molecular Formula	:	C4H11NO3
CAS Name	:	Tris (hydroxymethyl) aminomethane

Producer related part

Company	:	The Dow Chemical Company
Creation date	:	11.11.2006

Substance related part

Company	:	The Dow Chemical Company
Creation date	:	11.11.2006
Status	:	
Memo	:	
Printing date	:	14.11.2006
Revision date	:	
Date of last update	:	14.11.2006
Number of pages	:	60
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

Type	:	manufacturer
Name	:	Dow Chemical, TERC
Contact person	:	Dr. William T. Stott
Date	:	27.08.2006
Street	:	1803 Building
Town	:	48674 Midland, MI
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	Dow Chemical, TERC Midland, MI

30.08.2006

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

Type	:	manufacturer
Name of plant	:	Dow Chemical
Street	:	
Town	:	Sterlington, Louisiana
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Data from handbook or collection of data.

13.11.2006 (1)

Type	:	manufacturer
Name of plant	:	Dow Chemical
Street	:	
Town	:	Ibbenburen
Country	:	Germany
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Email	:	
Homepage	:	
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Data from handbook or collection of data.

13.11.2006 (1)

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name : 2-Amino-2-hydroxymethyl-1,3-propanediol
Smiles Code : OCC(N)(CO)CO
Molecular formula : C4H11NO3
Molecular weight : 121.14
Petrol class :

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

09.11.2006 (2)

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type : typical for marketed substance
Substance type : organic
Physical status : solid
Purity :
Colour : White
Odour : Odorless

Reliability : (2) valid with restrictions
Data from handbook or collection of data.

13.11.2006 (3)

1.1.2 SPECTRA

Type of spectra : NMR

Result : 13-Carbon NMR spectra of TRIS were measured between 407 and 461 K.
Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (4)

1.2 SYNONYMS AND TRADENAMES

Talatrol

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

19.03.2004 (2)

THAM

Source : Dow Chemical, TERC Midland, MI

Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

Trimethlol aminomethane

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

TRIS

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

TRIS AMINO ®

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
10.11.2006 (2)

Tris Buffer

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

Tris(hydroxymethyl)aminomethane

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

Tris-steril

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

Trisamine

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

Trizma

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

Trometamol

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

19.03.2004 (2)

Tromethane

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

09.11.2006 (2)

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value :

Remark : The compound is sold as 100% crystal or a 40% aqueous solution of tris(hydroxymethyl)aminomethane.
Source : MSDS of the Dow Chemical Company. 2003.
Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

09.11.2006

1.4 ADDITIVES

Purity type : typical for marketed substance
CAS-No : 7732-18-5
EC-No : 231-791-2
EINECS-Name : water
Molecular formula : H2O
Value : ca. 40 % v/v
Function of additive : Solvent

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

09.11.2006 (1)

1.5 TOTAL QUANTITY

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : use
Category : other: Emulsifier for cosmetics, mineral oil and wax emulsions, leather dressings, textiles, cleaners, pharmaceuticals, and chemical intermediate buffer

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

10.11.2006 (1) (2)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Result : May be prepared by reduction or catalytic hydrogenation of corresponding nitro compound. Preparation by electrolytic reduction: McMillan, US Patent 2,485,982 (1949 TO COMM SOLVENTS CORP), CA 44, 1836B (1950)
Source : Hazardous Substances Data Bank.
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

13.11.2006 (5)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

Type : degradation product
CAS-No :
EC-No :
EINECS-Name :

IUCLID Chapter :

Remark : THAM is stable at room temperature for periods as long as 12 years.
Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (6)

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Source of exposure : Human: exposure by production
Exposure to the : Substance

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

09.11.2006 (1)

Source of exposure : Human: exposure through intended use
Exposure to the : Substance

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

09.11.2006 (1)

Source of exposure : Human: exposure of the consumer/bystander
Exposure to the : Substance

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

09.11.2006 (1)

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 03.11.2006

13.11.2006

1.13 REVIEWS

2.1 MELTING POINT

Value : ca. 171 - 172 °C
Sublimation :
Method :
Year : 1989
GLP :
Test substance : as prescribed by 1.1 - 1.4

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
19.03.2004 (2)

Value : ca. 171 - 172 °C
Sublimation :
Method :
Year : 1940
GLP :
Test substance : as prescribed by 1.1 - 1.4

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.
24.03.2004 (7)

2.2 BOILING POINT

Value : ca. 219 - 220 °C at 101.33 hPa

Remark : @ 10mmHg
Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Data from handbook or collection of data.
28.06.2004 (2)

Value : ca. 219 - 220 °C at

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.
24.03.2004 (7)

2.3 DENSITY

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : ca. .000003 hPa at 25 °C
Decomposition :

Method	:	other (calculated)
Year	:	2004
GLP	:	
Test substance	:	
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Accepted calculation method.

28.06.2004 (8)

2.5 PARTITION COEFFICIENT

Partition coefficient	:	octanol-water
Log pow	:	= -2.31 at 20 °C
pH value	:	
Method	:	OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year	:	1996
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Conclusion	:	The calculated partition coefficient is consistent with high water solubility and which by definition would be indicative of low log Kow values.
Reliability	:	(1) valid without restriction Comparable to a guideline study.

13.11.2006 (9)

Partition coefficient	:	octanol-water
Log pow	:	<= -3.8 at 20 °C
pH value	:	
Method	:	OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year	:	1997
GLP	:	no data
Test substance	:	other TS:AMPD
Test substance	:	AMPD (2-Amino-2-methyl-1,3-propanediol) CAS# 000115-69-5. Molecular weight = 105.14

13.11.2006 (10)

Partition coefficient	:	octanol-water
Log pow	:	ca. -2.22 at °C
pH value	:	= 7
Method	:	other (calculated)
Year	:	2004
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Model Input Parameters:

Data Temperature (°C) = 25
Chemical Type = 1
Molecular Mass (g/mol) = 121.14
Water Solubility (g/m3) = 550,000
Vapor Pressure @ 25° C (Pa) = 3.0 x 10-4
Melting Point (C) = 171.5
Estimated Henry's Law Constant (H) (Pa m3/mol) = 6.7 x 10-8
Log Kow (Octanol-Water Partition Coefficient) = -2.22 / 1.38
Simulated Emission (kg) = 100,000

Conclusion	:	This material has very high water solubility, very low vapor pressure, and very low log Kow. In the absence of advective and reactive processes, these physical properties dictate that the material will partition exclusively to the water compartment at equilibrium.
Reliability	:	(2) valid with restrictions Accepted calculation method.

07.04.2004 (11)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in	:	Water
Value	:	ca. 800 g/l at 25 °C
pH value	:	
concentration	:	at °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	8.03 at 25 °C
Description	:	
Stable	:	
Reliability	:	(2) valid with restrictions Data from handbook or collection of data.

13.11.2006 (12)

Solubility in	:	Water
Value	:	ca. 550 other:mg/mL at 25 °C
pH value	:	ca. 10.4
concentration	:	.1 other:Molar at 25 °C
Temperature effects	:	
Examine different pol.	:	
pKa	:	at 25 °C
Description	:	
Stable	:	
Deg. product	:	
Method	:	
Year	:	1989
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Data from handbook or collection of data.

19.03.2004 (2)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

Acid-base constant	:	8.21
Method	:	
Year	:	1989
GLP	:	
Test substance	:	
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Data from handbook or collection of data.

28.06.2004 (13)

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

Memo	:	pKa= 8.3 @ 20°C; 8.03 @ 25°C; 7.8 @ 37°C
Source	:	L. Troester (2006) ANGUS data.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data.

13.11.2006

3.1.1 PHOTODEGRADATION

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at °C
t1/2 pH7	:	at °C
t1/2 pH9	:	at °C
Deg. product	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Conclusion	:	TRIS AMINO is stable for several years at ambient temperatures according to ANGUS files.
Reliability	:	(2) valid with restrictions Data from handbook or colletion of data.

13.11.2006 (14)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	water - air
Air	:	% (Fugacity Model Level I)
Water	:	100 % (Fugacity Model Level I)
Soil	:	% (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: calculated Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada.
Year	:	2006
Result	:	Tris(hydroxymethyl)aminomethane has high water solubility, a low vapor pressure, and low log Kow. The substance has a low potential for adsorption to soil or sediments, and a low potential to volatilize from water or soil to the atmosphere. If released to air, the substance will react with hydroxyl radicals. If released directly to water, the most probable emission route based on physical properties and use patterns, most of the substance will remain in the water compartment and is expected to be biodegraded. If released to soil, the substance is expected to be biodegraded.
Test condition	:	Input Parameters for Level I Model: Data Temperature (°C) = 25 Chemical Type = Type 1 indicates chemical can partition into all

environmental compartments
Molecular Mass (g/mol) = 121
Water Solubility (g/m3) = 8.0 x 10^5
Vapor Pressure @ 25° C (Pa) = 3.0 x 10^-4
Melting Point (°C) 171.5
Estimated Henry's Law Constant (H) (Pa m3/mol)= 4.54 x10^-8
Log Kow Octanol-Water Partition Coefficient = -2.3
(Estimated value of Log D at pH 7.0 / Estimated value for neutral species)
Simulated Emission (kg) = 100,000 (Level I Default Value)

Input parameters to Level III Model:

Data Temperature (°C)=25 Default environmental temperature
Chemical Type= Type 1 indicates chemical can partition into all environmental compartments
Molecular Mass (g/mol)= 121
Water Solubility (g/m3)= 8.0 x 10^5
Vapor Pressure @ 25°C (Pa)= 3 x 10^-4
Melting Point (°C)= 171.5
Henry's Law Constant (Pa*m3/mole)= 4.54 x10^-8
Log Kow (Octanol-Water Partition Coefficient)= -2.3
Simulated Emission Rate (kg/hr)= 1,000

Simulated Environment Level III Default environment
Reaction Half-lives (hr) Input to Level III Model:
Air (vapor phase) 4
*Water (no susp. solids) 3600
*Soil 7200
*Sediment 7200
**Suspended Sediment 1.0 x 10^11
**Fish 1.0 x 10^11
**Aerosol 1.0 x 10^11

*Half-lives extrapolated based on inherent biodegradability classification, according to Technical Guidance Document of the European Commission.
**Default value used in Level III model when reaction is expected to be negligible in this compartment.

Reliability : (2) valid with restrictions
Accepted calculation method.

14.11.2006 (15)

Type : fugacity model level III
Media : water - air
Air : 0 % (Fugacity Model Level I)
Water : 100 % (Fugacity Model Level I)
Soil : 0 % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method :
Year : 2002

Result : This material has very high water solubility, very low vapor pressure, and very low log Kow. These properties dictate that the material has low potential to volatilize from water or soil to air, or adsorb to soil and sediments from the dissolved state. When released to water (the most likely emission scenario), the material will remain dissolved in water and is expected to be ultimately biodegraded. If released to soil, the material will be primarily dissolved, and remain mobile in, soil pore water (groundwater).
Source : Dow Chemical, TERC Midland, MI
Test condition : Input Parameters for Level I Model:

Data Temperature (°C) = 25

Chemical Type = Type 1 indicates chemical can partition into all environmental compartments
Molecular Mass (g/mol) = 121.14 C
Water Solubility (g/m3) = 550,000
Vapor Pressure @ 25° C (Pa) = 3.0 x 10-4
Melting Point (C) 171.5
Estimated Henry's Law Constant (H) (Pa m3/mol) = 6.7 x 10-8
Log Kow Octanol-Water Partition Coefficient = -2.22 / 1.38 (Estimated value of Log D at pH 7.0 / Estimated value for neutral species)
Simulated Emission (kg) = 100,000 (Level I Default Value)
Estimated Henry's Law Constant (H) = (Pa m3/mol) 6.7 x 10-8

Reaction Half-lives (hr.) Input to Level III Model
Air (vapor phase) 3.8
Water (no susp. solids) 3600
Soil 7200
Sediment 7200
Suspended Sediment 1.0 x 10^11
Fish 1.0 x 10^11
Aerosol 1.0 x 10^11

Reliability : (2) valid with restrictions
Acceptable calculation method.

09.11.2006 (16)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1990
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Conclusion	:	TRIS AMINO is not readily biodegradable.
Reliability	:	(1) valid without restriction Meets national standard methods (AFNOR/DIN).

13.11.2006 (17)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	other: aerated and static were both tested
Species	:	other:29 species were tested
Exposure period	:	
Unit	:	
Method	:	
Year	:	1958
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Fish were exposed to the buffer for 2 days, then placed in untreated water and observed for 30 days. Fresh-water species were left in the buffer solutions for 9 days. The vessels were tested under static and aerated conditions separately. Fish were monitored for signs of toxicity.
Result	:	Increases in weight occurred in all species. The pH decline over the 9 day fresh-water test was 0.02 pH units. One specimen of chiclid (Aquidens portalegrensis) died during the third day, likely die to starvation since none were fed until the fourth day. There was no other mortality in any other fish throughout the study period. The only observations of toxicity noted were to specimens of the opaleye (Girella nigricans), which exibited a marked interruption of opercular movements after 5 hours in the TRIS buffer. Irregularities appeared in solutions ranging from 5-20g TRIS per gallon water. The irregularities were characterized by two or three large opercular beats, followed by a pause lasting 5-10 seconds. Total beats varied from 8-20 per minute. The upset in opercular rhythm did not seem to have an adverse effect upon the fish. They appeared normal in all other aspects.
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	The following marine species were tested: Heterodontus francisci Holocentris microstomus Myripristis murdjan Pseudopeneus bifasciatus Amphiprion percula Lepidaplois bilunulatus Iniistius pavo Girella nigricans Kuhlia marginatus Hippocampus punctulatus Hepatus olivaceus Hepatus bariene Microcanthis strigatus Zebrasoma flavescens Zanclus canescens Heterostichus rostratis Leptocottus armatus Clinocottus analis Balistes vidua The following fresh water species were tested: Lebistes reticulatus Mollienesia sp. Aequidens portalegrensis Cichlasoma nigrofasciatus
Conclusion	:	Tests indicate that 29 species of fish can stand high concentrations of buffer (20g / gallon) dissolved in transport water. Light dosages (2-5g / gallon) are adequate to stabilize pH during transport of fish, regardless of

the presence of aeration (provided the weight of fish transported does not exceed 25-50g / gallon in a closed system). The data indicate that TRIS buffer is nontoxic to the 29 species tested under these conditions.

Buffered solutions are stable for up to three months at normal air temperatures.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (18)

Type : static
Species : Brachydanio rerio (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : > 10000 measured/nominal
Method : OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year : 1997
GLP :
Test substance : other TS:AMPD

Result :

Hour	LC50 (mg/L)
24	>10000
48	>10000
72	>10000
96	>10000

Test substance : AMPD: 2-Amino-2-methyl-1,3-propanediol
Conclusion : The acute LC50 96-hour for Brachydanio rerio is > 10,000 mg/L for AMPD.
Reliability : (2) valid with restrictions
Guideline study with acceptable restrictions.

14.11.2006 (19)

Type :
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : > 10000 calculated
Method :
Year : 1990
GLP :
Test substance : as prescribed by 1.1 - 1.4

Source : IWL labs 1990
Conclusion : The 96-h LC50 in golden orfe is >10,000 mg/L.
Reliability : (2) valid with restrictions
Data from handbook or collection of data.

13.11.2006 (20)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type :
Species : Crangon crangon (Crustacea)
Exposure period : hour(s)
Unit : mg/l
LC50 : = 179 measured/nominal
Method :
Year : 1983
GLP : no data
Test substance : other TS: AMP

Test substance	:	AMP-95 (2-Amino-2-methyl-1-propanol)
Conclusion	:	The 48- & 96-hour LC50 values for Crangon crangon is 179 mg/L.
Reliability	:	(2) valid with restrictions

13.11.2006 (21)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
EC50	:	= 193 measured/nominal
Method	:	
Year	:	1980
GLP	:	no data
Test substance	:	other TS:AMP

Test substance	:	AMP95 (2-Amino-2-methyl-1-propanol)
Conclusion	:	In Daphnia magna, AMP-95 was reported with a 48-hour EC50 of 193 mg/L.
Reliability	:	(2) valid with restrictions

13.11.2006 (22)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	4 day(s)
Unit	:	µg/l
NOEC	:	ca. 100 measured/nominal
Method	:	
Year	:	1985
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Dilutions of the actively-growing cultures were added to test flasks to give an approximate initial count of 1000 cells per mL, and incubated 24 hours. An appropriate volume of test material was added to achieve the desired concentration, and the culture volume made up to 100mL with particle-free deionized water. Cell counts were made every 24 hours. The cell counts were used to calculate the growth parameters to establish quantitative toxic values.
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Stock cultures of Selenastrum were maintained at 22C under constant illumination from 2 fluorescent tubes, on slopes of Oxoid agar containing Bold's basal medium. About 7 days prior to use, 2 conical flasks of 90mL particle-free BBM were aseptically inoculated with Selenastrum from stock cultures. The cultures were incubated at 22C, and shaken at 175 rpm under constant illumination. Sub-cultures were made into fresh medium 2 days prior to inoculation of the test flasks, and incubated under identical conditions.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (23)

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	96 hour(s)
Unit	:	µg/l
NOEC	:	ca. 100 measured/nominal
Method	:	

Year	:	1985
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Dilutions of the actively-growing cultures were added to test flasks to give an approximate initial count of 1000 cells per mL, and incubated 24 hours. An appropriate volume of test material was added to achieve the desired concentration, and the culture volume made up to to 100mL with particle-free deionized water. Cell counts were made every 24 hours. The cell counts were used to calculate the growth parameters to establish quantitative toxic values.
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Stock cultures of Selenastrum were maintained at 22C under constant illumination from 2 fluorescent tubes, on slopes of Oxoid agar containing Bold's basal medium. About 7 days prior to use, 2 conical flasks of 90mL particle-free BBM were aseptically inoculated with Selenastrum from stock cultures. The cultures were incubated at 22C, and shaken at 175 rpm under constant illumination. Sub-cultures were made into fresh medium 2 days prior to inoculation of the test flasks, and incubated under identical conditions.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (23)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	
Unit	:	mg/l
EC10	:	ca. 33447 measured/nominal
Method	:	other: Acute Bacteia Cell Multiplication Inhibition Test
Year	:	1990
GLP	:	yes
Test substance	:	other TS: TRIS AMINO 40%
Method	:	A small amount of bacteria from a 7-day old stock culture of Pseudomonas putida was inoculated in fluid nutrient medium in Erlenmeyer flasks. The preliminary cultures were incubated at 25°C for 16-20 hours. Subsequently, the extinction of the monochromatic radiation at 436 nm for a 10 mm layer of the bacterial suspension was determined by photoelectric measurement. On the basis of the values measured, the final turbidity value if the bacterial suspension was adjusted. Four parallel dilution series in 300 ml Erlenmeyer flasks stoppered with aluminium caps were prepared from the formulated test substance stock solution and sterile Milli-Q water. Each flask contained 80 ml of liquid at the start. Each flask of three dilution seried to be inoculated, was made up to a final volume of 100 ml by adding 5 ml of a stock solution I, 5 ml of a stock solution II, and 10 ml of the prepared bacterial suspension from the preliminary culture having a known adjusted extinction value. The flasks of the dilution series that are not inoculated, were made up to 100 ml by adding 5 ml of stock solution I, 5 ml of stock solution II, and 10 ml of saline. Five culture flasks of the reference series were made up with 80 ml of the

methanol concentration, 5 ml stock solution I, 5 ml stock solution II, and 10 ml prepared bacterial solution.

Ten control culture flasks with 80 ml sterile Milli-Q water, 5 ml stock solution I, 5 ml stock solution II and 10 ml prepared bacterial solution were also included.

All flasks were left at 25°C for 16-20 hours. Subsequently, cell suspensions were homongenized and the extinction of the monochromatic radiation at 436 nm in a 10 mm layer in all series were measured.

Because, after termination of the test period, coloration or turbidity occurred in the dilution series for chemical-physical reasons, the analogous steps of dilution of the non-inoculated series were used as photometric blank values for turbidity fo the inoculated dilutions series.

Remark : The study procedure was based on the following guideline: Umweltbundesamt (UBA) Guidelines: wassergefährdender Stoffe, III Bestimmung der akuten Bakterientoxizität, ad-hoc-Arbeidsgruppe I (Obmann Dr. Niemitz), LTWS, Nr. 10, September 1979.

Result : TRIS AMINO 40% was investigated for its ability to inhibit the cell multiplication of the bacteria species Pseudomonas putida. Cultures of Pseudomonas putida bacteria were exposed to concentrations ranging from 432 to 885.6x10^3 TRIS AMINO 40% per litre. Based on the solubility of TRIS AMINO 40% in water, a toxicity threshold value of TRIS AMINO 40% of 33.4x10^3 mg/l for Pseudomonas putida could be determined.

Conclusion : The Assessment figure or value for bacteria toxicity is 1.5.

Reliability : (1) valid without restriction
GLP guideline study.

13.11.2006 (24)

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period :
Unit : mg/l
EC10 : = 400 measured/nominal
EC50 : = 1600 measured/nominal
Method : DIN 38412, part8
Year : 1990
GLP : no data
Test substance : other TS: TRIS AMINO 40%

Result : EC50 = 1600 mg/l
EC10 = 400 mg/l

Test condition : Concentrations (g/l): 10, 5, 2.5, 1.25, 0.625 and 0.315
Temperature: 20-22°C

Reliability : (2) valid with restrictions
Meets national standard methods with acceptable restrictions.

13.11.2006 (25)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Value	:	ca. 5000 ml/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	10
Vehicle	:	
Doses	:	10000, 7000, 5000, 3500 and 2000 mg/kg bw
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Ten mice per dose were administered TRIS AMINO solutions via gavage at a constant volume of 0.05 ml/gm bw.
Conclusion	:	The oral LD50 in mice is 5500 mg/kg.
Reliability	:	(2) valid with restrictions Meets national standard methods with acceptable restrictions.

13.11.2006 (26)

Type	:	LD50
Value	:	> 3000 mg/kg bw
Species	:	other: rat and mice
Strain	:	other:Wistar and Swiss
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	1000, 2000, and 3000 mg/kg as a solution
Method	:	
Year	:	1962
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Solutions of 20% and 5% of TRIS AMINO were given via gastric intubation to rats and mice respectively at doses of 1000, 2000, and 3000 mg/kg.
Result	:	There was no toxicity noted in either species at the top dose levels, although abundant urine output was noted for some animals
Conclusion	:	The LD50 for rats and mice are estimated to be >3000 mg/kg in solution.
Reliability	:	(2) valid with restrictions

13.11.2006 (27)

Type	:	LD50
Value	:	ca. 3350 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	
Doses	:	7000, 5000, 3530, 2500, and 2000 mg/kg bw
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	other TS:AMPD

Test substance	:	AMPD: 2-Amino-2-methyl-1-propanol
Reliability	:	(2) valid with restrictions Meets national standard methods with acceptable restrictions.

13.11.2006 (26)

5.1.2 ACUTE INHALATION TOXICITY

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Value	:	> 1000 mg/kg bw
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	5
Vehicle	:	
Doses	:	500 mg/kg (delivered via 5% solution)
Method	:	
Year	:	1962
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Five rats were injected with 500 or 1000 mg/kg (via 5% solution) of THAM.
Result	:	500 mg/kg caused irritation at the injection site. 1000 mg/kg caused the formation of lesions. There were no other observations noted.
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (27)

Type	:	LD50
Value	:	> 1000 mg/kg bw
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	5
Vehicle	:	
Doses	:	
Method	:	
Year	:	1962
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Mice were injected with 500 or 1000 mg/kg THAM (via 5% solution).
Result	:	500 mg/kg caused irritation at the injection site. 1000 mg/kg caused skin lesions at the site. There were no other observations of toxicity noted.
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (27)

Type	:	LD50
Value	:	> 2000 mg/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	male/female
Number of animals	:	12
Vehicle	:	other: no vehicle
Doses	:	1000, 1500, and 2000 mg/kg
Method	:	other: Pharmacology Lab Protocol
Year	:	1980
GLP	:	yes
Test substance	:	other TS:AMP
Method	:	Each group of rabbits was treated with 1000, 1500, or 2000 mg of test material per kg body weight (mg/kg). The desired dose was spread over the prepared abdominal skin area (abraded or smooth as designated). The skin was covered with a gauze and a sheet of impervious rubberized cloth to prevent any loss of the test material. The trunk was further enclosed with a flexible wire screen held in place by tape. The animals were returned to individual cages. After 24 hours dermally exposed, the bindings and patches were removed, the exposed areas gently cleaned, and observed for skin irritancy. The animals were observed for another 14 days for any gross symptoms of toxicity. At the end of the 14 day observation period, the animals were weiged, sacrificed, and the organs examined for gross pathology.
Result	:	At the end of the 24 hour exposure period, the intact and abraded treated skin sites were severely irritated and black in color. The sites became necrotic within two to three days and remained necrotic for the 14 days. The treated sites had severe eschar formation by the 14th day. The rabbits in the three treatment groups lost body weight over the 14 day observation period. The animals in all treated groups showed no signs of toxicity or abnormal pharmacological behavior. At necropsy, all organs in all rabbits were grossly normal. The treated skin sites in all rabbits were necrotic.
Test condition	:	12 Rabbits weighing 3.0 +/- 0.5 kg were divided into 3 groups of 4 each, and their abdomens were shaved free of hair. The skin of 2 rabbits were further prepared by abrasions. The abrasions were made 2-3 cm apart over the area of exposure with a blunt hypodermic needle without bleeding.
Test substance	:	AMP:2-Amino-2-methyl-1-propanol; CAS# 124-68-5; molecular formula C4H11NO; molecular weight 89.14
Conclusion	:	The acute dermal LD50 for P-1826 for the rabbit was >2000 mg/kg. The test material was dermally nontoxic, but was a severe skin irritant.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable assessment.

13.11.2006 (28)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	LD50
Value	:	ca. 3350 ml/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	
Doses	:	4000, 3600, 3250, 2500 and 2000 mg/kg bw
Route of admin.	:	i.p.

Exposure time	:	96 hour(s)
Method	:	
Year	:	1955
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Ten mice per dose were administered TRIS AMINO solutions via intraperitonal at a constant volume of 0.015 ml/gm bw.
Conclusion	:	The acute LD50 i.p. of TRIS AMINO is 3350 mg/kg bw.
Reliability	:	(2) valid with restrictions Meets national standard methods with acceptable restrictions.

13.11.2006 (26)

Type	:	LD50
Value	:	ca. 16.5 other: mM TRIS/kg
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	10
Vehicle	:	no data
Doses	:	
Route of admin.	:	i.v.
Exposure time	:	.5 minute(s)
Method	:	
Year	:	1961
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	IV injections of Tris over 30 seconds using un-neutralized and neutralized solutions of 0.3M Tris.
Result	:	The LD50 = 16.5 mM Tris / kg Mice that were given a lethal dose convulsed immediately before death.
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Ten mice for each dose, injected IV. Mice were observed for 24 hours and LD50 calculated from the per cent of mice that died.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (29)

Type	:	LC50
Value	:	3.28 - 4.04 other:g/kg
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	6
Vehicle	:	physiol. saline
Doses	:	2.0, 2.5, 3.0, 3.5 g/kg of 0.6M THAM, 4.0 and 4.5 g/kg of 0.9M THAM.
Route of admin.	:	i.v.
Exposure time	:	1 minute(s)
Method	:	
Year	:	1965
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Group 1 Males and females (3 rats each sex) were administered various doses of THAM via the tail vein. The dose levels of THAM administered were 2.0, 2.5, 3.0, 3.5 g/kg of 0.6M THAM, 4.0 and 4.5 g/kg of 0.9M THAM. Group 2 A replication of experiments conducted with Group 1. Instead of administering a single given dose level of THAM, to all rats in one unit in

one day, the different dosage levels were given at one sitting to pairs of rats, and repeated, on subsequent days, until all 36 animals in this group had been used. Ultimately, 3 male and 3 female rats from Group 2 received THAM at each of the dosage levels shown for Group 1.
Group 3
As a partial control (to rule out adverse effects of rapid infusions of large volumes of fluid), 4 pairs of male and female rats received IV infusions, via the tail vein, of physiological saline (0.9g NaCl per 100mL). The infusion rates and volumes of saline were similar to the fluid infusion rates and volumes required for each dose level of THAM.

In all cases, the rate of administration of the test solutions was established individually based each rat's body weight. Each animal received the test material such that they receive 0.45g THAM per kg body weight would be administered in one minute. Sterile equipment was used throughout the study, and each animal was treated with a separate syringe and needle. Animals that survived the infusions were held and observed for 2 hours post-infusion and were sacrificed and necropsied. Necropsies were likewise performed on animals dying spontaneously following treatment. Specimens from all organs and tissues were preserved, embedded, and stained. All histopathologic and histochemical methods were performed according to established methods.

Result : In most cases, rats that did not survive the post-infusion period died during the infusion or very soon afterward. Those animals that survived longer than 10 minutes following treatment survived the entire post-infusion period and recovered with no grossly-observable ill effects. All 8 control animals survived the infusion.
There were no significant gross lesions noted at necropsy for any of the animals, with the exception of the liver and kidneys. Peracute toxic nephrosis was noted consistently in the kidneys up to 2 hours post-infusion. The lesion varied in that it was limited to a moderate degree to pyknosis of the nuclei of isolated segments of the renal tubular epithelium in rats infused with 2 and 2.5 g/kg THAM doses, and increased in severity with the dose. In higher dose levels, the lesions were characterized by severe pyknosis of the nuclei of swollen renal tubular epithelial cells of carried segments of the cortex. The cytoplasm of the affected cells was coagulated, distinctly granular, and intensely eosinophilic. Lumens of the affected tubules were distended with eosinophilic, amorphous tissue debris and secretions. Affected tubules were observed adjacent to apparently normal tubules. The incidence of lesions increased with increasing dose levels, and were noted in a similar dose-response pattern in animals dying spontaneously or at scheduled sacrifice.

Lethargy was noted sporadically in rats at 3 -4 g/kg dose levels. There were all noted with lesions of acute toxic hepatitis. The lesion was characterized by pyknosis of the nuclei of the hepatocytes and cloudy swelling of the cytoplasm of hepatocytes. Although the lesions are thought to be related to THAM administration, they did not constitute a consistent characteristic lesion as did the peracute toxic nephrosis.

Source : Dow Chemical, TERC Midland, MI

Test condition : Eighty, 200-300g Sprague-Dawley rats (males & females) were observed for 14 days prior to study start for health evaluation. They were segregated into 3 groups: 2 experimental groups of 36 animals each (18 males and 18 females), and one control group (4 males and 4 females).

Conclusion : The actual LD50 of THAM given intravenously was calculated to be 3.5 g/kg +- 0.1 for Group 1, and 3.6 g/kg +- 0.2 for Group 2. Statistical evaluation calculated a maximum likelihood estimate of 3.55 and 3.64 g/kg of body weight respectively, with a fiducial probability of 95%. The value of LD50 in groups 1 and 2 were expected to be 3.28-3.83 g/kg and 3.28-4.04 g/kg, respectively.

A NOAEL was not observed. Observations, treatment-related, were noted

at the lowest dose level tested.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (30)

Type : LC50
Value : ca. 6000 mg/kg bw
Species : rat
Strain :
Sex :
Number of animals : 10
Vehicle :
Doses : 100, 200, 400, 500, 1000, 3000, 5000, 6000, 7000 mg/kg (1 & 20% solutions)
Route of admin. : i.v.
Exposure time :
Method :
Year : 1962
GLP :
Test substance : as prescribed by 1.1 - 1.4

Result : There were no notations of any toxicity at doses lower than 3000 mg/kg. At 5000 mg/kg, 30% mortality was noted, at 6000 mg/kg, 60% mortality was noted, and at 7000 mg/kg, 70% mortality was noted.
Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (27)

Type : LC50
Value : ca. 6100 mg/kg bw
Species : mouse
Strain :
Sex :
Number of animals : 10
Vehicle :
Doses : 100, 200, 400, 500, 1000, 2000, 3000, 5000, 6000, 7000 mg/kg (1% solution)
Route of admin. : i.v.
Exposure time :
Method :
Year : 1962
GLP :
Test substance : as prescribed by 1.1 - 1.4

Result : There was no mortality noted at doses less than 5000 mg/kg. At 6000 mg/kg, 40% mortality was noted, and at 7000 mg/lg, 100% mortality was recorded. Animals experienced muscle weakness accompanied by respiratory difficulty prior to death.
Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (27)

Type : LC50
Value :
Species : rabbit
Strain :
Sex :

Number of animals	:	5
Vehicle	:	
Doses	:	250, 500 mg/kg (5% solution)
Route of admin.	:	i.v.
Exposure time	:	
Method	:	
Year	:	1962
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Marginal vein in the ear was used.
Result	:	There was no treatment-related mortality. Changes in respiratory rate and amplitude were the only observations noted.
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (27)

Type	:	LC50
Value	:	> 125 ml/kg bw
Species	:	dog
Strain	:	
Sex	:	
Number of animals	:	5
Vehicle	:	
Doses	:	125 mg/kg (5% solution)
Route of admin.	:	i.v.
Exposure time	:	
Method	:	
Year	:	1962
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Saphenous vein was used.
Result	:	Alterations in respiratory rate and amplitude were the only observations noted.
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (27)

Type	:	LD50
Value	:	> 3000 mg/kg bw
Species	:	rat
Strain	:	Wistar
Sex	:	
Number of animals	:	10
Vehicle	:	
Doses	:	
Route of admin.	:	other: gastric tube
Exposure time	:	
Method	:	
Year	:	1962
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Method	:	Doses of 1000 and 3000 mg/kg were administered by gastric tube in a 20% solution.
Result	:	There were no signs of acute toxicity noted.

Abundant urine output was recorded for some animals.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (27)

Type : LD50
Value : > 3000 mg/kg bw
Species : mouse
Strain : Swiss
Sex :
Number of animals : 10
Vehicle :
Doses :
Route of admin. : other: gastric tube
Exposure time :
Method :
Year : 1962
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Doses of 1000, 2000, and 3000 mg/kg were delivered by gastric tube in a 5% solution.
Result : There was no significant toxicity noted, other than increased urine output.
Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (27)

5.2.1 SKIN IRRITATION

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
Vehicle :
PDII :
Result : moderately irritating
Classification :
Method : Draize Test
Year : 1961
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : A saturated solution (pH 10.8), 25% solution, and the crystalline product were tested on intact and abraded skin of rabbits.
Result : The saturated solution and the crystalline product produced comparable primary irritation scores. There was no noticeable irritation produced by any of the test concentrations on unabraded skin. All signs of irritation were completely resolved in 48 hours.

Solution	Intact	Abraded	Total
crystals	0	0.83	0.4
saturated	0.16	0.83	0.5
25% soln	0	0.16	0.08

The test material is considered a mild irritant to the skin.

Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(4) not assignable Documentation insufficient for assessment.
09.11.2006		(31)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
Vehicle	:	
PDII	:	
Result	:	highly irritating
Classification	:	irritating
Method	:	Draize Test
Year	:	1975
GLP	:	no
Test substance	:	other TS:AMP

Source	:	ANGUS Chemie GmbH Ibbenburen European Commission - European Chemicals Bureau Ispra (VA).
Test substance	:	AMP: 2-Amino-2-methyl-1-propanol; Molecular formula C4H11NO; Molecular weight 89.14
Reliability	:	(4) not assignable Documentation insufficient for assessment.
13.11.2006		(32)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	6
Vehicle	:	none
Result	:	not irritating
Classification	:	not irritating
Method	:	
Year	:	1975
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Result	:	Combined Average Score = 0/110 Classification = Non-irritating
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(4) not assignable Documentation insufficient for assessment.
13.11.2006		(33)

Species	:	rabbit
Concentration	:	40 %
Dose	:	
Exposure time	:	
Comment	:	
Number of animals	:	6
Vehicle	:	water
Result	:	not irritating
Classification	:	not irritating

Method	:	
Year	:	1992
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Source	:	L. Troester (2006). Personal communication.
Reliability	:	(2) valid with restrictions Data from handbook or collection of data.

13.11.2006 (34)

5.3 SENSITIZATION

Type	:	Intracutaneus test
Species	:	guinea pig
Concentration	:	1st: Induction .1 % 2nd: Challenge .05 % 3rd: Challenge .01 %
Number of animals	:	30
Vehicle	:	water
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	
Year	:	1982
GLP	:	
Test substance	:	other TS:AMP

Method : One group was treated with 0.05mL of 1% P-1826 solution, a negative control group was treated with saline, and a positive control group was treated with dinitrochlorobenzene (DNCB solubilized in alcohol and made to volume with saline). After 24 hours, sites were cleaned and scored for erythema and edema according to Draize (Draize, JH, "Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics". Assoc. of Food and Drug Officials of the United States, p. 48, 1957). At 48 hours, the application was repeated with each group, and continued 2-3 times per week until 10 applications were made. Animals were allowed a 2 week recovery period, and then challenged at a virgin site. The test and negative control animals were challenged with 0.1mL of 0.05% and 0.01% solutions of P-1826. Positive and negative control animals were also challenged with 0.3% and 0.03% DNCB solution. After 24 hours, they were depilated, and three hours later scored for erythema and edema. Sites were scored again at 48 hours.

Test material is considered a sensitizer if the challenge elicits skin reactions in a large number of test animals when compared to the negative control.

Result : During the induction phase, the first injection at 1% and second injection at 0.5% P-1826 induced necrotic lesions, so the remaining 8 injections were made with 0.1% solutions. The 0.3% DNCB sites were necrotic for the entire 10 injections.

At challenge with 0.05% and 0.01% P-1826, one animal in the test group showed mild reactions with 0.05%, but none of the negative controls challenged with P-1826 showed any reactions at 24 or 48 hours. In the repeat challenge, none of the animals in the test group showed any reactions with P-1826, but of the negative control group, 4 animals at 0.05% and 1 animal at 0.01% showed skin reactions at 24 hours.

A challenge with the positive control induced skin reactions in the positive control group. The 0.03% solution did not elicit any skin reaction at 48 hours.

Test condition	:	Thirty male guinea pigs (250-300g each) were divided into 3 groups of 10 each. The animals' backs and flanks were shaved free of hair. The guinea pigs were intradermally-injected with the solutions.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

14.11.2006 (35)

Type	:	Patch-Test
Species	:	guinea pig
Concentration	:	1st: Induction 5 % 2nd: Challenge 2.5 % 3rd: Challenge 5 %
Number of animals	:	30
Vehicle	:	water
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	other: Buehler
Year	:	1982
GLP	:	
Test substance	:	other TS: AMP

Method : : One group was treated with 0.5mL of 10% P-1826 solution, a negative control group was treated with saline, and a positive control group was treated with dinitrochlorobenzene (DNCB solubilized in alcohol and made to volume with saline). After 24 hours, the patches were removed, and sites were cleaned and scored at 24 and 48 hours for erythema and edema according to Draize (Draize, JH, "Appraisal of the Safety of Chemicals in Foods, Drugs, and Cosmetics". Assoc. of Food and Drig Officials of the United States, p. 48, 1957). At 48 hours, the application was repeated with each group, and continued 2-3 times per week until 10 applications were made. Animals were allowed a 2 week recovery period, and then challenged at a virgin site. The test and negative control animals were challenged with 0.5mL of 2.5% and 5% solutions of P-1826. Positive and negative control animals were also challenged with 0.03% DNCB solution. After 24 hours, the test material was cleaned away, depilated, and three hours later scored for erythema and edema. Sites were scored again at 48 hours.

Test material is considered a sensitizer if the challenge elicits skin reactions in a large number of test animals when compared to the negative control.

Result : During the induction, the 10% P-1826 solution was found to be mildly irritating to all animals in the test group, so the remaining 8 doses during the induction were made with a 5% solution. The positive control, DCNB, elicited a mild to strong reaction during the 10 applications. There was one death in the positive control group, but was deemed not treatment-related via necropsy.

At challenge with 2.5% and 5% solutions of P-1826, none of the animals in the test or positive control groups showed any skin reactions at 24 hours, but the positive control animals showed mild skin reactions at 48 hours.

Nine of ten positive controls when challenged with DNCB at 24 hours showed skin reactions, and 7/10 showed reactions at 48 hours. Only 4/10 negative controls showed reactions when challenged with DNCB at 24 hours, and none at 48 hours.

Test condition : Thirty male guinea pigs (250-300g each) were divided into 3 groups of 10 each. The animals' backs and flanks were shaved free of hair. The guinea pigs were topically treated with the solutions applied under an occlusive patch.

Conclusion : 2-Amino-2-methyl-1-propanol was a non-sensitizer in the topical

sensitization test in guinea pigs, under these test conditions.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

14.11.2006 (36)

Type : other
Species : human
Number of animals :
Vehicle :
Result :
Classification :
Method :
Year :
GLP : no data
Test substance : other TS: AMPD and AMP

Result : In patch tests with humans, cosmetic formulations containing either 0.22% AMP or 0.5% AMPD or 0.075% AMPD were negative for dermal sensitization.

Test condition : AMP
The skin irritation potential of a cosmetic formulation containing 0.22% AMP-95 was examined using a single insult occlusive patch test on 15 panelists. One panelist formulation containing 0.22% AMP-95 had a negligible primary skin irritation potential.

AMPD
A cosmetic formulation containing 0.073% AMPD was tested for sensitization potential in a group of 30 human test subjects using a repeated insult open patch test. The material was applied to the arm daily 4 days/week for 2 weeks, alternating arms daily. In addition, an occlusive patch was was applied on the first day of the test. After the 2-week application period, there was a 2-week nontreatment period. After this 2-week period, the test subjects received a reapplication of the formulation of the formulation to the test site along with an occlusive patch at an adjacent site. The original patch, challenge patch, and open challenge test sites were read at 24, 48, and 96 hour. No reactions were observed in any of the test subjects. The formulation containing 0.073% AMPD was neither a primary irritant, nor a fatiguing agent, nor a sensitizer, and the formulation was safe under the conditions of the study.

A modified repeated insult patch test of a cosmetic formulation containing 0.5% AMPD was performed on a panel of 39 women and 20 men. The test material, 0.5 ml, was applied to a semiopen patch on the arm of each panelist every Monday, Tuesday, Wednesday, and Thursday for two weeks. The patch sites were graded approximately 24 h after application. In addition, a closed patch was applied to each panelist on the first day fo the study and on the day of challenge. No patches were applied for 2 weeks after the induction phase. On Monday following the nontreatment period, challenge patches were applied to the original test site and an adjacent site; the second closed patch patch was also applied at this time. The challenge sites were graded 1, 2, and 4 days after application. Slight erythema was noted at one adjacent applicatin site at each of the grading times, but it was clear whether these reactions occurred in the panelist. The formulation containing 0.5% AMPD was not a sensitizer under the conditions fo the test.

Reliability : (2) valid with restrictions
Data from handbook or collection of data

14.11.2006 (37) (38)

5.4 REPEATED DOSE TOXICITY

Type	:	Sub-chronic
Species	:	rabbit
Sex	:	
Strain	:	
Route of admin.	:	i.v.
Exposure period	:	1-99 days
Frequency of treatm.	:	once daily
Post exposure period	:	
Doses	:	5-100 mL of 0.3M Tris per kg bodyweight, given at pH 7.4 and at pH 5.5
Control group	:	
Result	:	Treatment-related mortality was first noted a few days after start of treatment. Results of the study indicate that neutralized Tris is less toxic. Toxic symptoms noted included anorexia, bloody urine, hindleg paralysis, and irregular respiration. Gross observations at necropsy included abnormally red lungs, necrosis at the point of infusion, bleached liver, darkened spleen, bloated stomach, and lesions on the heart and kidney. Histological examinations of the organs were negative. Blood sampling following treatments with TRIS indicated that the levels increased upon successive treatments, and remained high the following day. Results indicate an accumulation of Tris at 25mL/kg (0.3M), the top dose evaluated for this parameter, but not at doses lower. Blood sampling following treatment with Tris (0.3M neutralized and non-neutralized) could not establish a direct relationship between Tris concentrations and glucose concentrations in the blood due to lost sampling data. The glucose concentrations, however, dropped significantly during the infusions, but returned to normal or above normal following the end of the infusions (Tris-induced hypoglycemia persisted longer than the Tris-neutralized). Tris and Tris-Neutralized both caused transient hypoglycemia. Blood analysis on extracted blood (Tris added to blood droplets at varying levels) also determined that there was no deleterious effect on erythrocytes. Urinalysis (urine collected via Foley catheter measured every hour for 7 hours following start of infusion) revealed that the amount of Tris excreted in the urine reached a maximum at the end of infusion, and dropped rapidly after infusion stopped. Only a small quantity of chloride was excreted. With Tris pH 5.5, a larger amount of chloride than with Tris was excreted. At the end of the 7 hours, 44% of the infused Tris was found in the urine, while with Tris pH 5.5, 77% was found. Causes of local necrosis around the infusion site were investigated using Tris pH 5.5 and 7.4. Using injected Trypan dye, the irritation caused by the solutions was evaluated by observing the amount of extravasated dye. Neutralization of the Tris reduced the irritation, suggesting that the pH of the Tris is the probable cause of the dermal irritation.
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Two or three rabbits for group, injected IV over 3-6 hours for 1-99 consecutive days (depending on the endpoint being measured) at a doses ranging 5-100 mL of 0.3M Tris per kg bodyweight. The doses were given at pH 7.4 and at pH 5.5 to investigate differences related strictly to pH.
Conclusion	:	1. Acute IV toxicity of 0.3M Tris is 55mL/kg. Neither neutralization of addition of glucose or NaCl decreases the toxicity. 2. Maximum subchronic non-lethal dose of 0.3M Tris in rabbits is 75-90mL/kg over 5 hours. Neutralization appears to decrease the toxicity. 3. If high doses of Tris are given frequently, Tris will accumulate. 4. Injection of Tris causes hypoglycemia during infusion and afterward. Tris neutralized causes hypoglycemia only during infusion. There is no direct relationship between Tris and glucose concentrations in the blood.

5. Dermal irritation is likely caused by pH, and not toxicity per se of Tris.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (29)

Type	:	Sub-acute
Species	:	rabbit
Sex	:	
Strain	:	
Route of admin.	:	infusion
Exposure period	:	10 days
Frequency of treatm.	:	once daily
Post exposure period	:	
Doses	:	
Control group	:	
Method	:	
Year	:	1961
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No treatment-related mortality was noted in either species. There were no toxic symptoms, and a histological study of the organs was negative.
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Three of each species for each dose, injected IV over 30 seconds for 10 consecutive days at a dosage of 50 mL and 10 mL of 0.155M Tris per kg bodyweight.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (29)

Type	:	Sub-chronic
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	oral feed
Exposure period	:	3 months
Frequency of treatm.	:	
Post exposure period	:	
Doses	:	0, 25, 150, 250, 2500 ppm in feed
Control group	:	yes, concurrent vehicle
LOAEL	:	= 2500 ppm
Method	:	
Year	:	1981
GLP	:	
Test substance	:	other TS:AMP
Remark	:	Results & methods sections referenced appendix data, which is not provided in Dow's copy of the report. As such, test material intake (mg/kg/day) could not be estimated.
Test substance	:	AMP-95/HCl 66.1ai (Lot 109-1)
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

13.11.2006 (39)

Type	:	Sub-acute
Species	:	rat
Sex	:	
Strain	:	Sprague-Dawley

Route of admin.	:	infusion
Exposure period	:	20 days
Frequency of treatm.	:	1 infusion daily
Post exposure period	:	24 hour or 7 day recovery period without infusions prior to necropsy
Doses	:	0.3M THAM (0.5, 1.5g/kg THAM: 10 or 20 infusions)
Control group	:	yes, concurrent vehicle
NOAEL	:	ca. 500 mg/kg
Method	:	
Year	:	1965
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4

Method :

Group 1
Twelve rats (6 each sex) were given 20 daily infusions via the tail vein of 0.3M THAM at 0.5 g/kg administered at 0.45g/kg/min.
Group 2
Twelve rats (6 each sex) were given 20 daily infusions via the tail vein of 0.3M THAM at 1.5 g/kg administered as a single injection in a 1-2 minute period.
Group 3
Twelve rats (6 each sex) were given 10 daily infusions via the tail vein of 0.3M THAM at 0.5 g/kg administered at 0.45g/kg/min. On the 11th day, the infusions were discontinued and IP injections were commenced at the same dose level. The IP injections were given daily for 10 days as a single injection in a 1-2 minute period.
Group 4
As controls, 4 rats (2 each sex) received 20 daily IV infusions, via the tail vein, of a solution containing 9g NaCl and 0.37g KCl per liter of water. The rate of injection was 1mL/kg/min.
Group 5
As controls, 4 rats (2 each sex) received 20 daily IP injections of a solution containing 9g NaCl and 0.37g KCl per liter of water. The rate of injection was 1mL/kg/min.

Half of the surviving rats of Group 1 & 2 and of the rats of the remaining groups were observed for 24 hours after the 20th infusion and were sacrificed and necropsied. The remaining rats of groups 1 & 2 were observed an additional 7 days post-infusion before a scheduled necropsy. At necropsy, tissue and organ specimens were taken, preserved, processed, and evaluated according to established histopathologic and histochemical methods.

Result : There were no findings noted in any animal in Group 1. Group 1 &3 animals experienced dry gangrene at the sites of the tail injections. Approximately half of the rats in Group 2 & 3 were noted with a mild inflammation of various parts of the visceral peritoneum, or fat necrosis and hemorrhage of the serosa of various parts of the stomach, intestine, and peritoneum. No gross lesions were noted in any control animal. Microscopic examination of tissues revealed a chronic cellulites at the injection sites, and peracute toxic nephrosis of the kidneys (5/6 rats of Group 1 necropsied 24 hours after injection, but not seen in animals allowed the 7 day recovery period). In group 2, all rats necropsied at 24 hours and 5/6 rats in the 7-day recovery group presented similarly.

Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Sprague-Dawley, 200-300g, rats (19 males & 19 females) were observed for 14 days prior to study start for health evaluation. They were segregated into 5 groups.
Conclusion	:	NOAEL = 0.5g/kg of 0.3M THAM
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (30)

Type	:	Sub-acute
Species	:	mouse
Sex	:	
Strain	:	
Route of admin.	:	infusion
Exposure period	:	10 days
Frequency of treatm.	:	once daily
Post exposure period	:	
Doses	:	
Control group	:	
Method	:	
Year	:	1961
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No treatment-related mortality was noted in either species. There were no toxic symptoms, and a histological study of the organs was negative.
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Three animals for each dose, injected IV over 30 seconds for 10 consecutive days at a dosage of 50 mL and 10 mL of 0.155M Tris per kg bodyweight.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (29)

Type	:	Sub-acute
Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	i.v.
Exposure period	:	4 weeks, 5 days per week
Frequency of treatm.	:	once daily
Post exposure period	:	24 hours or 20 day recovery periods
Doses	:	0.3M THAM at 0.5g/kg at a rate of 0.5 mL/min.
Control group	:	yes, concurrent vehicle
Method	:	Group 1 Each animal in the first group was given 20 daily infusions (5 days per week for 4 weeks) of 0.3M THAM at 0.5g/kg at a rate of 0.5 mL/min. Group 2 Animals were given 20 daily IV infusions of normal saline to which 5 m Eq of KCl were added per liter. The dosage and rate of administration were equal in volume and time, on a kg bodyweight basis, to the first group. Two males and 2 females from each group were sacrificed and necropsied within 24 hours of the completion of the last treatment. The remaining animals in each group were held for an additional 20 days post-infusion prior to necropsy. Bodyweight, food and water intake, and urine output were recorded daily, urinalysis weekly. Rectal temperature was recorded twice daily during the pre- and post-infusion periods, and immediately before and hourly until temperatures returned to normal after all infusions given over the 20 day treatment period. Urinalysis (pH, albumin, glucose, benzidine test for hemoglobin on centrifuged sediment and supernate, and microscopic examination for red and white blood cells and casts) was performed on the first urine voided after infusions during the 20 day treatment period on the first day of infusions, and twice a week for the remaining 3 weeks. Two days a week during the infusion period, a post-infusion urinary THAM excretion was measured on 2 males and 2 females in each group. Heart blood specimens were collected for BSP retention tests once during the pre- and post-infusion weeks and during the second week of the infusion period. Blood specimens were collected from an ear

vein for the following tests, once during the pre- and post-infusion periods and twice a week during the infusions: total serum proteins, A/G ratios, serum bilirubin, cephalin flocculation, and serum transaminase. Also, blood specimens were collected at the same time for hemoglobin and hematocrit determinations, and for white blood cell, red blood cell, differential, and platelet counts.
At necropsy, specimens from all organs and tissues were extracted, preserved, and examined grossly and microscopically. Histochemical examinations were performed on liver and kidney specimens fixed in formalin-calcium for the following: alkaline phosphatase, acid phosphatase, esterase, peptidase, DPN diaphorase, and PPN diaphorase.

Result : Food and water consumption and body temperature was not effected by treatment in any group, nor was water diuresis produced. Body weight fluctuated throughout study in all animals, including control, but not in any treatment-related pattern. Seven of 8 rabbits receiving THAM had inflammatory lesions of the external ear. The lesions carried from swelling and redness to dry gangrene and erosion.
Weekly analyses on blood samples were normal for the following parameters: total serum proteins, A/G ratio, serum bilirubin, cephalin flocculation, serum transaminase, RBC, differential counts, hemoglobin, microhematocrit, and platelet counts. White blood cell counts in excess of 13,000 were seen in 5/8 rabbits receiving THAM. In all cases, elevated WBC coincided with the observations of dry gangrene in the external ear. No significant findings were noted in any of the parameters tested during urinalysis.
No gross lesions were noted in control animals at necropsy, however 2/4 test rabbits necropsied 20 days post-infusion presented grossly visible infarcts in the kidneys. No gross lesions were noted in any other organ or tissue in any other animal.
In 7/8 test animals in which there were gross lesions of the ear, there were microscopic lesions of chronic cellulites and necrosis at sites of injection in the subcutaneous tissues of the ear. The gross kidney lesions in the 2 animals were confirmed microscopically. They were also found to have chronic interstitial nephritis. Infiltrations of lymphocytes were seen in tissue sections of the liver and kidney of 3 additional test rabbits. The infiltrations were seen in animals that were allowed to recover 20 days post-infusion, as well as those sacrificed immediately following the treatment series.
Peracute toxic nephrosis was observed in 1 rabbit, which also presented urolithiasis. Lesions of peracute toxic nephrosis were not observed in any of the other 7 rabbits receiving THAM.

Source : Dow Chemical, TERC Midland, MI

Test condition : New Zealand rabbits (16 adult, 3-4kg) were used. After a 2 week observation period, the animals were segregated into 2 groups composed of 4 male and 4 female animals per group.

Conclusion : Other than the necrotizing effects at the injection site, and transient body temperature changes, the IV administration of up to 20 daily doses of 0.5g/kg of 0.3M THAM produces no readily detected deleterious effects in mature rabbits.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (30)

Type : Chronic
Species : dog
Sex : male/female
Strain : Beagle
Route of admin. : oral feed
Exposure period : 1 year
Frequency of treatm. : Continuous
Post exposure period :
Doses : 0, 1.1, 11, 110 ppm

Control group	:	yes, concurrent vehicle
NOAEL	:	> 110 ppm
Method	:	
Year	:	1990
GLP	:	
Test substance	:	other TS: AMP-HCl (47.1% AMP)

Remark : Test material intake is estimated based on week 36 body weights and food consumption.

Males

	estimated (mg/kg/day)
Control	0
1.1ppm	.031
11ppm	0.31
110ppm	2.98

Females

	estimated (mg/kg/day)
Control	0
1.1ppm	.029
11ppm	0.31
110ppm	2.55

Test substance	:	2-amino-2-methyl-1-propanol supplied by Angus Chemical Co, Northbrook, IL. Supplied as an aqueous solution of AMP-HCl. Concentration of AMP in the solution was 47.1%.
Conclusion	:	Based on the findings under these study conditions, there is no effect at any dose level on general appearance, behavior, body weight, food consumption, ophthalmoscopic exams, clinical chemistry, hematology, organ weights, or tissue histopathology. Based on the absence of statistically and biologically significant findings in dose-response patterns, the No-Observed Effect Level for AMP in the diets of Beagle dogs in greater than 110 ppm.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

13.11.2006 (40)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Gene mutation in Saccharomyces cerevisiae
System of testing	:	
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	
Year	:	1990
GLP	:	
Test substance	:	other TS

Result	:	No evidence of ketorolac tromethamine-induce mutagenesis in in vitro Saccharomyces cerevisiae [Syntex Laboratories, Inc. Toradol IM (ketorolac tromethamine) prescribing information, product monograph and formulary facts. Palo Alto, CA; 1990]
Source	:	Dow Chemical, TERC Midland, MI
Test substance	:	Ketorolac is commerically available as the tromethamine salt. Ketorolac tromethamine is commercially available as a racemic mixture.

Reliability	:	(4) not assignable Documentation insufficient for assessment.
13.11.2006		(41)
Type	:	Bacterial gene mutation assay
System of testing	:	E.coli
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	negative
Method	:	
Year	:	1990
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No evidence of ketorolac tromethamine-induce mutagenesis in in vitro Escherichia coli [Syntex Laboratories, Inc. Toradol IM (ketorolac tromethamine) prescribing information, product monograph and formulary facts. Palo Alto, CA; 1990]
Source	:	Dow Chemical, TERC Midland, MI
Test substance	:	Ketorolac is commerically available as the tromethamine salt. Ketorolac tromethamine is commercially available as a racemic mixture.
Reliability	:	(4) not assignable Documentation insufficient for assessment.
13.11.2006		(41)
Type	:	other: Mechanism of nucleolysis in DMA
System of testing	:	Streptomyces lividans
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	:	
Result	:	positive
Method	:	
Year	:	1992
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	The authors investigated reactivity using a test system of electrophoretic activation of electrophoresis buffer conponents and a combination of the activated samples with S.lividans plasmid DNA. After termination of the reaction, DNA samples were assayed for double-strand cleavage. The assay involved gel electrophoresis of the DNA samples in HEPES buffer, components of which are non-reactive with the DNA modifications, Southern transfer, and hybridization.
Result	:	The authors conclude that two finctional groups of TRIS are involved in strand scission. Initial electrophoretic activation at the anode is absolutely required for the formation of a TRIS derivative, a presumptive oxygen-centered radical species which can be scavenged by thiourea. This species reacts with the DNA modifications in the first instance. As a result, the lesions are then susceptible to further attack, resulting in strand cleavage. The authors infer that it is the amine group in particular which confers on TRIS its nucleolytic activity.
Source	:	Dow Chemical, TERC Midland, MI
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.
09.11.2006		(42)
Type	:	Salmonella typhimurium reverse mutation assay
System of testing	:	
Test concentration	:	
Cycotoxic concentr.	:	

Metabolic activation	:	
Result	:	negative
Method	:	
Year	:	1990
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No evidence of ketorolac tromethamine-induce mutagenesis in in vitro Salmonella typhimurium [Syntex Laboratories, Inc. Toradol IM (ketorolac tromethamine) prescribing information, product monograph and formulary facts. Palo Alto, CA; 1990]
Source	:	Dow Chemical, TERC Midland, MI
Test substance	:	Ketorolac is commerically available as the tromethamine salt. Ketorolac tromethamine is commercially available as a racemic mixture.
Reliability	:	(4) not assignable Documentation insufficient for assessment.

13.11.2006 (41)

5.6 GENETIC TOXICITY 'IN VIVO'

Type	:	Micronucleus assay
Species	:	mouse
Sex	:	
Strain	:	
Route of admin.	:	
Exposure period	:	
Doses	:	
Result	:	negative
Method	:	
Year	:	1990
GLP	:	
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	There was no evidence of mutagenicity when the micronucleus assay was used to test for chromosome breaks in vivo mice that had received ketorolac tromethamine [Syntex Laboratories, Inc. Toradol IM (ketorolac tromethamine) prescribing information. Palo Alto, CA; 1990]
Source	:	Dow Chemical, TERC Midland, MI
Test substance	:	Ketorolac is commerically available as the tromethamine salt. Ketorolac tromethamine is commercially available as a racemic mixture.
Reliability	:	(4) not assignable Documentation insufficient for assessment.

13.11.2006 (41)

5.7 CARCINOGENICITY

Species	:	dog
Sex	:	male/female
Strain	:	Beagle
Route of admin.	:	oral feed
Exposure period	:	1 year
Frequency of treatm.	:	continuous
Post exposure period	:	
Doses	:	0, 1.1, 11, 110 ppm
Result	:	negative
Control group	:	yes, concurrent vehicle
Method	:	
Year	:	1990

GLP :
Test substance : other TS: AMP-HCl (47.1% AMP)

Remark : Test material intake is estimated based on week 36 body weights and food consumption.

Males

	estimated (mg/kg/day)
Control	0
1.1ppm	.031
11ppm	0.31
110ppm	2.98

Females

	estimated (mg/kg/day)
Control	0
1.1ppm	.029
11ppm	0.31
110ppm	2.55

Test substance : 2-amino-2-methyl-1-propanol supplied by Angus Chemical Co, Northbrook, IL. Supplied as an aqueous solution of AMP-HCl. Concentration of AMP in the solution was 47.1%.

Conclusion : Based on the findings under these study conditions, there is no effect at any dose level on general appearance, behavior, body weight, food consumption, ophthalmoscopic exams, clinical chemistry, hematology, organ weights, or tissue histopathology. Based on the absence of statistically and biologically significant findings in dose-response patterns, the No-Observed Effect Level for AMP in the diets of Beagle dogs in greater than 110 ppm.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

13.11.2006 (40)

Species : Syrian hamster
Sex : male
Strain :
Route of admin. : other: intratracheal
Exposure period :
Frequency of treatm. :
Post exposure period :
Doses :
Result : negative
Control group : yes, concurrent vehicle
Method :
Year : 1979
GLP : no data
Test substance : other TS: TRIS AMINO and 0.9% NaCl

Method : Thirty 8-week old male Syrian golden hamsters were used in the control group. The animals received a pelleted diet and water ad libitium. Weekly intratracheal instillations of a 0.2 ml mixture of TRIS buffer and 0.9% NaCl were performed for the life of the hamster.

Animals were observed for life or sacrificed when moribund. Body weights, average survival time and tumor incidence for the respiratory tract (trachea, larynx and lungs) were analyzed. Complete necropsies were performed and the organs fixed in a 10% buffered formalin.

Result : TRIS AMINO did not induce tumors when tested in male Syrian golden hamsters.

13.11.2006 (43)

5.8.1 TOXICITY TO FERTILITY

Type	:	other
Species	:	rat
Sex	:	male/female
Strain	:	other:CD
Route of admin.	:	oral feed
Exposure period	:	Males were exposed for at least two weeks prior to breeding & throughout breeding for 37 days. Females were exposed for 2 weeks prior to breeding, continuing through breeding (up to 2 weeks), gestation (3 weeks), & lactation (4 days).
Frequency of treatm.	:	
Premating exposure period		
Male	:	At least two weeks prior to breeding.
Female	:	Two weeks prior to breeding
Duration of test	:	
No. of generation studies	:	
Doses	:	100, 300, or 1000 mg/kg/day
Control group	:	yes, concurrent no treatment
Method	:	OECD Guide-line 421
Year	:	2005
GLP	:	yes
Test substance	:	other TS:AMP
Method	:	Male and female CD rats were fed diets supplying 0 (control), 100, 300, or 1000 mg/kg/day of AMP-HCL. Males were exposed for at least two weeks prior to breeding and continuing throughout breeding for 37 days. The females were exposed for two weeks prior to breeding, continuing through breeding (up to two weeks), gestation (three weeks), and lactation (four days). Effects on gonadal function, mating behavior, conception, development of the conceptus, parturition, litter size, pup survival, sex, pup body weight, pup gross external morphological alterations, and pathology of adult gonads were assessed.
Result	:	Increases in absolute and relative liver weights, accompanied by a very slight degree of microvacuolization of periportal hepatocytes, with or without vacuolization of hepatocytes were noted in males. Females in all treatment groups exhibited similar histopathological changes in the liver, but in the absence of an organ weight change. AMP had no effect on mating performance or conception, but caused marked, dose-related increases in post-implantation loss (embryo resorption). At the high dose level, all 12 pregnant females showed evidence of complete litter resorption (100% post-implantation loss), while at 300 mg/kg/day, post-implantation loss was 70% (vs. 10% in controls). Effects associated with, or secondary to the post-implantation loss increase at 300 mg/kg/day included decreased litter size, increased pup body weight, and decreased gestation body weight and body weight gain. There were no treatment related effects on reproductive performance in the 100 mg/kg/day group.
Test substance	:	Chemical Name: 2-Amino-2-methyl propanol hydrochloride salt Molecular Formula: C4H11NO Molecular Weight: 89.14 Synonyms: AMP, AMP-HCL
Conclusion	:	The NOEL for general toxicity in males was 300 mg/kg/day, while the general toxicity for females could not be determined, based on the presence of very slight microscopic liver effects. The NOEL for reproductive effects was considered to be 100 mg/kg/day.
Reliability	:	(1) valid without restriction GLP guideline study

13.11.2006 (44)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	
Route of admin.	:	dermal
Exposure period	:	6 hours daily day from gestation days (GD) 6-20
Frequency of treatm.	:	daily
Duration of test	:	from gestation days (GD) 6-20
Doses	:	30, 100, or 300 mg AMP/kg/day
Control group	:	yes
NOAEL maternal tox.	:	= 100 mg/kg bw
other: NOEL for developmental Tox.	:	= 300 mg/kg bw
Result	:	There was no evidence of test article related systemic maternal or developmental toxicity at any dose level tested.
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	2006
GLP	:	yes
Test substance	:	other TS:AMP

Method : Female rats were exposed 6 hours daily dermally to 0, 30, 100, or 300 mg AMP/kg/day from gestation days (GD) 6-20 (Carney and Thorsrud, 2006). Rats were sacrificed on GD 21, and subjected to a pathological examination including examination of the external tissues and all orifices, stomach, liver, kidneys, and uterine findings. The first four presumed pregnant females from each dose group were selected for blood collection to evaluate systemic exposure following dermal administration of AMP on the last day of dosing (GD 20).

Result : Dermal administration of 300 mg/kg/day of AMP produced significant effects at the test site, as evidenced by scabbing and moderate to severe scaling. The dermal finding of slight scaling at 30 and 100 mg/kg/day was not considered adverse, as the observation was transient in nature and relatively low in incidence. There was no evidence of test article related systemic maternal or developmental toxicity at any dose level tested. Analyses of blood samples confirmed systemic exposure to AMP in a dose-responsive manner, although the study was not designed to quantify percent absorption.

Test substance :
CAS Number: 124-68-5
IUPAC Name: 2-Amino-2-methyl-1-propanol
Molecular Formula: C4H11NO
Molecular Weight: 89.14
Synonyms: AMP, AMP-95

Conclusion : Under the conditions of this study, the NOAEL for maternal toxicity based on dermal effects was 100 mg/kg/day. The NOEL for developmental toxicity was 300 mg/kg/day, the highest dose level tested.

Reliability : (1) valid without restriction
GLP study.

13.11.2006 (45)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

Endpoint : other: Dermal Absorbtion

Study descr. in chapter	:	
Reference	:	Wepierre, J. and Noel-Hudson, M.S.
Type	:	
Species	:	other: human skin
Sex	:	
Strain	:	
Route of admin.	:	100 uL applications to the skin.
No. of animals	:	
Vehicle	:	
Exposure period	:	24 hour(s)
Frequency of treatm.	:	once
Doses	:	0.1% and 10% solutions
Control group	:	
Observation period	:	
Result	:	less than 1% of applied dose is absorbed into the skin.
Method	:	
Year	:	1993
GLP	:	
Test substance	:	other TS: C-14 labeled Tromethamine hydrochloride

Method :

In vitro percutaneous absorption was studied using dermatomized human skin (obtained from plastic surgery biopsies of the abdomen and frozen until use) placed in Franz diffusion cells to permit contact of the dermis with a preservation liquid of sodium chloride and bovine serum albumin. The skin was thawed, defatted, and cut to 0.3mm thickness. A cutaneous biopsy is maintained horizontally between the dermis and epidermis. The system is surrounded with a warm water jacket to maintain the temperature at 37C. The air and liquid in the system are circulated continuously to insure consistent temperature.

The test material, C-14- labeled tromethamine hydrochloride, was furnished by L'Oreal under the same S1 (0.1%) and S2 (10%). The test material (100 uL) was applied to 0.635 cm^2 skin. At regular time intervals (2, 4, 6, 8, 10 hours), the totality of the liquid contained in the dermal compartment is taken by lateral adjustment and replaced by new liquid. At t=24 hours, the preservation liquid is removed and the surface of the biopsy is washed with 100 uL of different solvents:
1st wash- Cetavlon / doubly-distilled water
2nd wash- doubly-distilled water
3rd wash- Cetavlon / doubly-distilled water
4th wash- doubly-distilled water
5th wash- doubly-distilled water
The application zone was wiped with cotton rolls, the dermis and epidermis were separated mechanically with a scalpel, and digested in Soluene TM for 24 hours at 37C.
The detection of remaining radioactivity was determined via liquid scintillation counter. The preservation liquid removed, cotton rolls, and glass cylinder are also counted for radioactivity. Counting values were corrected by the method of external standard to obtain the dpm.

Result :

Absorption of the test material is low and variable from one skin sample to another. At the end of 24 hours, 0.506 +- 0.765 for the 0.1% solution and 0.797 +- 0.691 for the 10% solution were determined. There is no significant difference between the percentages, showing that the increase in test material concentraion does not alter cutaneous permeability under these test conditions.
The fluxes in the 2 cases reaches a maximum value after 4 hours and remain constant during the rest of the experiment. After washing, the retention of tromethamine hydrochloride in the dermis and epidermis is low (0.13-0.14% for the 2 solutions in the epidermis and 0.69- 0.22% in the dermis). The test material is not retained in the horny layer. The washing waters contained more than 90% of the applied dose.

Source : Dow Chemical, TERC Midland, MI

Conclusion	:	Percutaneous absorption through human skin in vitro is low, on average less than 1% of the applied dose remains at the end of 24 hours, and the finding is independent of the concentration of tromethamine hydrochloride applied. The test material is almost totally eliminated by washing the skin after 24 hours. The test material is not retained in the horny layer.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (46)

5.10 EXPOSURE EXPERIENCE

Type of experience	:	Direct observation, clinical cases
Method	:	THAM (36g in 5% dextrose water) was infused in 4 of the subjects over a period of 30 minutes to 24 hours. One patient received 9g THAM over 30 minutes.
Result	:	In all cases, there was a substantial rise in the blood pH and a significant increase in the total CO2 content of the blood. However, none of the patients showed any clinical improvement. The increase in blood pH and total CO2 content appeared to persist for >48 hours in most of the patients and continued to remain elevated for a period of several days in 2 of the patients. Three of five patients showed 2 major complications following THAM administration: hyperkalemia and oliguria.
Source	:	Dow Chemical, TERC Midland, MI
Test condition	:	Five patients manifesting 3 types of renal disease: postpartum bilateral renal cortical necrosis, acute and chronic glomerulonephritis, and diabetic intracapillary glomerulonephrosclerosis. All subjects had severe impairment of renal functions as manifested clinically by oliguria, elevated blood urea nitrogen, and abnormal urinary findings. Two were anuric and 2 others were oliguric.
Conclusion	:	In 2 of the cases of complications, the subjects were acutely ill and manifested a severe renal failure that could have resulted in the hyperkalemia and oliguria. However, the third patient, who received the THAM administration more rapidly than the other 4 patients, presented initially with normal urine output and normal serum potassium, and within 12 hours of THAM administration showed marked oliguria and hyperkalemia and an elevation of blood urea nitrogen level, although the mechanism of such complications was not known at the time of publication. THAM is an effective agent in the prompt correction of metabolic acidosis. In comparison with sodium bicarbonate or lactate, it may also offer the advantage of being able to buffer the intracellular hydrogen ion. THAM may therefore be a more suitable agent to correct acidosis when sodium intake is a concern. The authors suggest a maximum dose of 500mg/kg (0.3M THAM in dextrose) given over 24 hours with careful monitoring of urinary output, serum potassium, and blood urea nitrogen for 48 hours following THAM administration.
Reliability	:	(2) valid with restrictions Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (47)

Type of experience	:	Direct observation, clinical cases
Remark	:	Results of this study (Samiy, et al., 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for

acidosis. The following reference supports the general findings of the authors of this article.
Authors support THAM's use as treatment of metabolic acidosis, noting generally positive outcomes and no adverse effects associated with THAM.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (48)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Samiy, et al., 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following reference supports the general findings of the authors of this article.
The authors support THAM as treatment of respiratory acidosis, and additionally noting a slight decrease in respiration rate following treatment.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (49)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Samiy, et al., 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following reference supports the general findings of the authors of this article.

For treatment of acidosis during cardiac bypass procedures and during total circulatory arrest, these authors additionally note that THAM is even more effective when CO2 is allowed a means to leave the blood (via respiration, etc), and can be used when sodium bicarbonate cannot be (when a patient is on total cardiopulmonary bypass). THAM has not been associated with any toxic effects and is rapidly excreted in the urine. It has however, been noted to have transient effects on blood sugar, serum potassium, increased urinary (water) loss, and depressed respiratory rates.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (50)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Samiy, et al., 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following reference supports the general findings of the authors of this article.

Authors note that Tromethamine NF is an effective blood buffer for metabolic and respiratory acidosis. They suggest administering sufficient amounts of water with treatment may prevent hyperosmolarity and avoid tissue dehydration, and that caution should be used to avoid hyperkalemia, hypoglycemia, and depression of the respiratory center.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (51)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Samiy, et al., 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following reference supports the general findings of the authors of this article.

Authors recommend THAM for treatment of diabetic acidosis, when patients are unable to tolerate sodium bicarbonate or lactate therapy due to severe cardiac and/or sodium-retaining renal failure. The authors suggest that THAM may reduce the insulin requirements for management of diabetic comas. The patients in this article, while responding favorably to THAM treatment, eventually succumbed to other complications of their conditions, and upon post-mortem examinations there were no findings that suggested THAM contributed to the causes of death.

Source : Dow Chemical, TERC Midland, MI

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (52)

Type of experience : Direct observation, clinical cases

Method : The patient breathes oxygen in a nonbreathing system to remove nitrogen from the lungs, after which a barbiturate is used to render the patient unconscious during the procedure. THAM is administered IV (0.33M solution in 0.2% NaCl) to investigate the buffering effect of THAM. Succinylcholine is injected and the bronchoscope introduced when the patient is completely paralyzed. Oxygen is continuously administered to the patients to ensure complete apneic oxygenation of the blood during the 6-minute procedure. Likewise, no carbon dioxide is allowed to exit the lungs. Arterial blood samples were drawn before and immediately following the 6-minute apneic period, and at 5 minutes and 2 hours post-procedure. All patients were maintained on ventilation until recovery of normal spontaneous respiration. Blood was analyzed for pH (one anaerobically and two at known CO2 tensions) and pCO2. Actual HCO3- was calculated according to Henderson-Hasselbalch fornula, and pO2 was determined with a modified Clark electrode. Brachial arterial blood pressure was measured using an inflatable cuff and mercury manometer.

Result : During the 6 minute procedure, the PaCO2 increased from 38 to 66 mmHg, with a fall in pH from 7.41 to 7.24 and a slight increase in actual bicarbonate from 24 to 28 mEq/L. When THAM was administered, the arterial pH was kept nearly constant, with a rise of almost identical proportions in H2CO3 and HCO3- in all cases. The PaCO2 rose from 37 to 42 mmHg and the HCO3- from 24 to 28 mEq/L. In all subjects, the arterial blood was completely saturated with oxygen throughout the procedure.

The two subjects in poor condition prior to the procedure were cyanotic when breathing air, however breathing pure O2 for 5 minutes relieved the cyanosis. Analysis of arterial blood in both subjects showed an almost-fully compensated respiratory acidosis. PaO2 during breathing suggested a shunting of nonoxygenated blood in the lungs. Six minutes of controlled ventilation pre-procedure increased the PaO2 slightly and caused a drop in PaCO2 to normal values with a marked alkaline shift in pH. Both faired similarly to the subjects in better initial health during the apneic period. Both showed improved respiratory status upon removal of secretions from the airways.

In patients not receiving THAM, there was a consistent rise in diastolic blood pressure, not seen when the respiratory acidosis was buffered with THAM. No patient receiving THAM reported any complaints or

complications that could be attributed to the buffer or the apnea.

Source : Dow Chemical, TERC Midland, MI

Test condition : Twelve adult subjects were treated with THAM in the study. The changes in acid-base status were compared with those occurring in 6 subjects not receiving THAM. Ten of the subjects had lung tumors or small tuberculous cavities and underwent bronchoscopy as a routine preoperative procedure. They were all in good general condition without respiratory distress. Two subjects, dealt with separately, were in poor condition with ventilatory insufficiency prior to the bronchoscopy.

Conclusion : Because all CO2 produced by the body remained in the body during the apneic period, a nearly-perfect stoichometric relationship was revealed between CO2 produced and the THAM needed to buffer it. The buffer was found to not only reduce the increase in arterial blood pressure, but also reduce the typical increase in cerebrospinal fluid pressure seen in respiratory acidosis. THAM was not found to cause any hypoglycemia, nor were any toxic manifestations noted following THAM treatment.
THAM is considered by the author to be helpful in counteracting respiratory acidosis especially in patients where a blood pressure rise or CSF pressure rise is not desired, during procedures where adequate ventilation cannot be maintained at all times.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (53)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Holmdahl, 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following references support the general findings of the authors of this article.

For treatment of respiratory acidosis caused by chronic alveolar hypoventilation, the following authors caution use of THAM, because, even though an effective buffer, they noted it caused in some patients an accentuation of anoxemia that became very severe, and suggested that THAM should not be used to treat such cases unless other means of oxygenation are supplied (mechanical aid). The authors do not support general use of THAM as a treatment for respiratory acidosis caused by chronic alveolar hypoventilation.

Source : Dow Chemical, TERC Midland, MI

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (54)

Type of experience : Direct observation, clinical cases

Result : Results of this study (Holmdahl, 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following reference supports the general findings of the authors of this article.

For treatment of respiratory acidosis, the authors likewise caution the use of THAM to buffer the blood unless supplemental oxygen is given due to a resulting decrease in minute ventilation rate. The authors advance the theory that the decrease in minute ventilation rate is due to the increase in pH of the blood and not due to a reduction of CO2 tension per se. They report spurious findings of kidney (swelling and hydropic degeneration of the lining of proximal tubules) and/or liver (hydropic degeneration of the cells) changes in 2 patients receiving THAM, however the authors are reluctant to attribute the findings directly to THAM based on others in their

sampling that do not present such signs.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (55)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Holmdahl, 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following reference supports the general findings of the authors of this article.

For treatment of respiratory acidosis, the authors find THAM an effective blood buffer, noting also a decrease in ventilation rate, and additionally a consistent rise in arterial blood pH and a considerable increase in urinary pH with an associated increase in urinary excretion of bicarbonate. They noted no adverse effects attributed to THAM treatment, and did not note hypoglycemia as other researches have, likely due to lower dose levels.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (56)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Holmdahl, 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following reference supports the general findings of the authors of this article.

For treatment of respiratory acidosis, the authors find THAM an effective blood buffer, noting also a decrease in ventilation rate, and additionally a consistent rise in arterial blood pH and a considerable increase in urinary pH with an associated increase in urinary excretion of bicarbonate. They noted no adverse effects attributed to THAM treatment, and did not note hypoglycemia as other researches have, likely due to lower dose levels.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (57)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Holmdahl, 1961) are typical of many publications evaluating clinical treatment of ill patients with THAM as a buffer for acidosis. The following reference supports the general findings of the authors of this article.

In the treatment of artificially-induced respiratory acidosis (in patients recovering from pulmonary tuberculosis with a normally sensitive respiratory center), THAM is found to be an effective buffer that prevents hyperventilation while breathing CO2. No toxicity has been noted, and respiratory toxicity was suggested by the authors to be unlikely due to rapidly-reversible effects on ventilation rates.

Source : Dow Chemical, TERC Midland, MI
Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (58)

Type of experience : Direct observation, clinical cases

Remark : Tromethamine occurs in Ketorolac Tromethamine at approximately 32% of the formulation to improve solubility. While it is not possible to differentiate the side effects of the active drug from Tromethane, there were no clinically-significant findings that would suggest it is inherently toxic.

Results of this study are typical of many publications evaluating clinical treatment of post-operative patients with Ketorolac Tromethamine.

Result : Ketorolac Tromethamine is a non-steroidal anti-inflammatory drug (NSAID) indicated for the treatment of acute pain, recently approved by the FDA (U.S. Food and Drug Administration) for IM (intramuscular) administration. It is a pyrrolo-pyrrole compound related to tolmetin and zomepirac. The tromethamine salt in Ketorolac enhances its solubility; there are 6.8mg ketorolac in 10mg ketorolac tromethamine.

Clinical trials of Ketorolac Tromethamine have produced positive analgesic effects in post-operative patients with quick onset of relief lasting longer than comparable doses of morphine. In addition, Ketorolac Tromethamine treatment provides a non dependency-forming alternative to opiates. Authors noted that some patients experienced a decreased platelet count and bleeding time that was statistically, but not clinically, significant, although it is not recommended for treatment of patients with existing bleeding disorders. It has, like most NSAIDS, the potential to cause gastric mucosal injury. Diarrhea, dizziness, sweating, and pain at the injection site were noted in 1-3% of patients. There have been no drug interactions noted. Although animal studies have shown no evidence of mutagenesis, carcinogenesis, or fertility impairment, it is not recommended for pregnant or lactating women. Respiratory depression has not been noted in patients using the drug.

While IM administration has been approved by the USFDA, intravenous administration was not approved when the article was published.

Source : Dow Chemical, TERC Midland, MI

Conclusion : Ketorolac Tromethamine has been evaluated by the USFDA to be a viable alternative to opiates for pain relief. While side-effects have been noted similar to other NSAIDS, it can be safely used as a non-habit forming drug to relieve pain in most patients.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (59)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Resman-Targoff, 1990) are typical of many publications evaluating clinical treatment of post-operative patients with Ketorolac Tromethamine. The following reference supports the general findings of the authors of this article.

Noting an increase in liver function test results, the following authors have additionally noted that the drug may not be ideal for use in patients with prior liver damage.

Source : Dow Chemical, TERC Midland, MI

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (60)

Type of experience : Direct observation, clinical cases

Remark : Results of this study (Resman-Targoff, 1990) are typical of many publications evaluating clinical treatment of post-operative patients with Ketorolac Tromethamine. The following reference supports the general findings of the authors of this article.

A transient renal insufficiency was noted by the following authors, directly attributed to Ketorolac Tromethamine treatment. Decreased urine output and an increased serum creatinine concentration were measured. There was no hyperkalemia noted. These observations, however, are in discord with observations of hyperkalemia and increased urine output noted with THAM infusion (minus Ketorolac) in other patients, suggesting that the observations noted by these authors could be primarily attributed to the Ketorolac.

Source : Dow Chemical, TERC Midland, MI

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

23.03.2004 (61)

Type of experience : Direct observation, clinical cases

Method : Four healthy adults received THAM via IV over 30-60 minutes in 0.03M NaCL / 0.005M KCl during 2.3 or 3.4% CO2 breathing.

Result : 64% of THAM administered was eliminated in the urine over 2 days, and 77% over 3 days.

Major side effects noted in the subject given 8.8 mM/kg bodyweight included: hypotension, hypoxia, hunger, sweating, periodic breathing, weakness, somnolence, diarrhea, intense wretching and vomiting, sensations of heat, swelling and numbness of face. In all other subjects, water diuresis was noted with decrease blood serum glucose concentrations. Urine pH and CO2 content rose as the THAM was eliminated.

Source : Dow Chemical, TERC Midland, MI

Reliability : (4) not assignable
Documentation insufficient for assessment.

24.03.2004 (62)

Type of experience : Direct observation, clinical cases

Method : Venous blood samples were taken from the other arm 10, 20, and 30 minutes after starting the infusion, and 5, 10, 20, and 40 minutes at 1, 2, 4, 8, 12, 20, and 24 hours after it had ended.

Urine was collected from the beginning of the infusion until 30 minutes after its end, from 30 min to 4 hours, from 4 to 8 hours, and from 8 to 24 hours.

Five patients required haemodialysis or haemofiltration as a result of acute anuria. In two patients, gastric juices were drained continuously via a plastic tube and were collected for 48 hours and analyzed for TRIS. In one patient, a drain had been implanted in the common bile duct diring choledocholithotomy and the bile was collected over two 24 hour periods.

All samples were analyzed for TRIS concentration via gas chromatography.

Result : In three patients, unidentified peaks were seen with the same retention times as TRIS due to additional medication. The haemofiltrates of these patients was subsequently not analyzed for TRIS concentrations.

The results from the 6 healthy subject were pooled. At the end of infusion, the TRIS plasma concentration averaged 565 ug/mL. There was a biexponential decline of plasma TRIS levels and after 24 hours, the level

was only 3.8 ug/mL. The half-life of the terminal phase was 5.6 hours. TRIS concentrations in erythrocytes rose more slowly, reaching a maximum 20 minutes after the end of infusions. After 2 hours, drug levels in erythrocytes were about 1.5 times greater than those in plasma, and they remained well above the corresponding plasma levels during the rest of the observation period.

Pharmacokinetic parameters were calculated from the individual concentration-time curves using a two-compartment model with elimination from the central compartment.

TRIS is mainly excreted by the kidney. Already 30 minutes after the end of infusion, 25% of the TRIS was found in the urine, and after 24 hours, 82% of the TRIS had been eliminated in that way.

Infusion of the strongly alkaline solution (pH 10.9) was well tolerated by all patients without adverse reactions.

The half-life of TRIS in normuric patients (including some with poor renal function) was longer than in healthy patients (16-45 hours), and the volumes of distribution were much larger. Up to 72% of the TRIS was eliminated in the urine after 24 hours, and an additional 2-5% excreted during the next 24 hours.

The half-life of TRIS in anuric patients ranged 15-58 hours. 25-66% of the infused TRIS left the plasma in the first 24 hours, and the clearance averaged 16.7 mL/kg/hr. Periods of haemodialysis or haemofiltration did not affect plasma TRIS level. The amount of TRIS eliminated via these procedures could not be measured as the fluid could not be collected for analysis.

Less than 0.2% of the infused dose of TRIS was found during 24 hours in gastric juice or bile.

Source : Dow Chemical, TERC Midland, MI

Test condition : Six healthy volunteers (5 males, 1 female, ages 27-37, weighing 50-90 kg) and 20 patients in a surgical intensive care unit (diagnoses ranged from traumatic lesions, intestinal bleeding, perforated appendicitis, and pancreatitis to rectal and gastric cancer, and aortic aneurysm) were infused with 121 mg/kg TRIS of 0.3 mol/L solution at a pH of 7.4 over 30 minutes in an antebrachial vein.

Conclusion : TRIS is primarily eliminated via the kidneys in the urine. There were no adverse effects related to TRIS treatment in any subject.

Accumulation of TRIS may occur in the body if patients with impaired renal funtion are repeatedly given TRIS treatment.

Reliability : (2) valid with restrictions
Meets generally accepted scientific standards, well-documented and acceptable for assessment.

09.11.2006 (63)

5.11 ADDITIONAL REMARKS

6.1 ANALYTICAL METHODS

6.2 DETECTION AND IDENTIFICATION

7.1 FUNCTION

7.2 EFFECTS ON ORGANISMS TO BE CONTROLLED

7.3 ORGANISMS TO BE PROTECTED

7.4 USER

7.5 RESISTANCE

8.1 METHODS HANDLING AND STORING

8.2 FIRE GUIDANCE

8.3 EMERGENCY MEASURES

8.4 POSSIB. OF RENDERING SUBST. HARMLESS

8.5 WASTE MANAGEMENT

8.6 SIDE-EFFECTS DETECTION

8.7 SUBSTANCE REGISTERED AS DANGEROUS FOR GROUND WATER

8.8 REACTIVITY TOWARDS CONTAINER MATERIAL

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10.1 END POINT SUMMARY

10.2 HAZARD SUMMARY

10.3 RISK ASSESSMENT