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	:	07.07.2009
Status	:	
Memo	:	
Printing date	:	07.07.2009
Revision date	:	
Date of last update	:	07.07.2009
Number of pages	:	71
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 : .0000027 hPa at 20 °C
Decomposition :

Method	:	ASTM method E1719-97
Year	:	2008
GLP	:	No
Test substance	:	
Source	:	Dow Chemical, Analytical Sciences, South Charleston, WV
Reliability	:	(1) valid without restriction

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 (assumes water is emission route, based on physical properties and use patterns)
Air	:	<0.1%
Water	:	100 %
Soil	:	<0.1%
Sediment	:	<0.1
Method	:	other: calculated Canadian Environmental Modeling Centre, Trent University, Peterborough, Ontario, Canada.
Year	:	2004

Result : Level III data is reported as follows:

Scenario	% to Air	% to Water	% to Soil	% to Sediment
1000kg/hr to Air	<0.1%	59.4%	40.6%	<0.1%
1000kg/hr to Water	<0.1%	100.0%	<0.1%	0.1%
1000kg/hr	<0.1%	58.3%	41.7%	<0.1%

to Soil

1000kg/hr <0.1% 68.6% 31.4% <0.1%
simultaneously to air, water, soil.

Conclusion : 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.

Source : Dow Chemical, TERC Midland, MI
Test condition : Input Parameters for Level III Model:

Data Temperature (°C) = 25
Chemical Type = Type 1 indicates chemical can partition into all environmental compartments
Molecular Mass (g/mol) = 121.14
Water Solubility (g/m3) = 800,000
Vapor Pressure @ 25° C (Pa) = 3.0 x 10-4
Melting Point (C) = 171.5
Estimated Henry's Law Constant (H) (Pa m3/mol) = 4.54 x 10-8
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) = 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**

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

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

09.11.2006 (15)

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
Results		No biodegradation measured after 28 days at test substance concentrations of 8.7 and 13 mg/L. : TRIS AMINO is not readily biodegradable.
Conclusion	:	
Reliability	:	(1) valid without restriction Meets national standard methods (AFNOR/DIN).

13.11.2006 (16)

Type	:	aerobic
Inoculum	:	activated sludge, domestic, non-adapted
Concentration	:	2 mg/l related to Test substance related to
Contact time	:	
Degradation	:	ca. 40 (±) % after 28 day(s)
Result	:	other: not readily biodegradable
Deg. product	:	
Method	:	OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test"
Year	:	1989
GLP	:	no
Test substance	:	Other: AMP

Method : The study followed OECD Guide-line 301 D "Ready Biodegradability: Closed Bottle Test".

AMP was dissolved in mineral nutrient medium at a concentration of 2 mg/L. The mineral medium had been prepared from aerated de-ionized water amended with nutrient salts and trace element stock solutions. The reaction mixtures were inoculated with a few drops of inoculum from the discharge of a community wastewater treatment plant. Corresponding control mixtures were prepared with the nutrient medium; nutrient medium with inoculum; and nutrient medium with inoculum and the reference substance sodium acetate to correct for background oxygen consumption and confirm the viability of the microbial inoculum. Equal volumes of the various reaction mixtures were dispensed into replicate bottles, sealed and incubated in the dark for 28 days at 20-21 ºC.

The dissolved oxygen concentration in duplicate samples was measured with an oxygen electrode on days 0, 5, 15, and 28. The percent biodegradation of the test substance was determined using the following formula:

$$Dt = \frac{(\text{mg of BODx/L}) \text{ o } 100}{(\text{mg of substance/L}) \text{ o TOD}}$$

Dt = percent biodegradation of the test substance
BODx = biological oxygen demand after x days.
TOD = Theoretical oxygen consumption

Result : The results for replicate samples, expressed as percent biodegradation, are as follows:

AMP: 5 days (0.1%, 0.1%); 15 days (1.9%, 1.9%); 28 days (40.7%, 38.9%)
Average biodegradation after 28 days was 40%.

Sodium acetate: 5 days (51.5%, 51.5%); 15 days (70.9%, 58.0%); 28 days (77.3%, 83.6%)

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

01.06.2006 (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)
Type : semistatic
Species : Pleuronectes platessa (Fish, marine)
Exposure period : 96 hour(s)
Unit : mg/l
LC50 : = 184 calculated
Method :
Year : 1983
GLP :
Test substance : other TS:AMP-95

Result : LC50 values were calculated to be the following, based on observed mortality, at a 95% Fiducial CI:
24 hour LC50 = 231 mg/L (138-385 mg/L)
48 hour LC50 = 184 mg/L (31-340 mg/L)
72 hour LC50 = 184 mg/L (31-340 mg/L)

96 hour LC50 = 184 mg/L (31-340 mg/L)

Nominal temperature of the test solution was 15C (14.4-15C during the test). Dissolved O2 range during the test was 7.0-8.2 mg/L. The pH range during the test was 8.1-10.3.

Test condition : In a 96-hour, semi-static seawater test system, the toxicity of AMP-95 to Plaice was studied. Fish (20 per dose level, mean weight of 4.1g and mean length of 63.2mm) were placed in 18L glass vessels containing 10L of the test solution. The pH of the system was 8.08-8.14, and salinity was 34.76-34.82 o/oo. Concentrations tested were 100, 320, 560, 1000 mg/L.

Reliability : (2) valid with restrictions
2e

19.03.2004 (21)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
LC0 : = 320
LC50 : = 331
LC100 : = 340
Method : other: DIN 38 412 L 15
Year : 1986
GLP :
Test substance : Other: AMP

Source : ANGUS Chemie GmbH Ibbenburen
European Commission - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable
4e

05.03.2004

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : semistatic
Species : Crangon crangon (Crustacea)
Exposure period : 96 hour(s)
Unit : mg/l
EC50 : ca. 179 calculated
Analytical monitoring : no data
Method :
Year : 1983
GLP :
Test substance : Other: AMP-95

Method : Concentrations of AMP-95 tested were 0, 56, 100, 320, and 560 mg/L under semi-static conditions for 96 hours. The 18L glass vessel was filled with 10L of the test solution, and 20 brown shrimp were added to each vessel after an on-site acclimation period of 5 days on a specially-prepared diet. Food was withheld during the test. The test solution was comprised of local filtered seawater (pH=8.10-8.16, salinity 34.86-34.90 o/oo), and was maintained within a temperature range of 14.7-15.8C. The solutions were aerated with compressed air and dissolved O2 ranged from 7.2-8.4 mg/L. The pH range during the test was 8.0-10.1.

Remark : Detailed information regarding pH and dissolved oxygen were not provided. Only target ranges were given.

Result : Results were as follows, with a 95% Fiducial CI:
24-hour LC50 = 241 mg/L (17.8-292 mg/L)
48-hour LC50 = 179 mg/L (98.2-329 mg/L)
72-hour LC50 = 179 mg/L (98.2-329 mg/L)
96-hour LC50 = 179 mg/L (98.2-329 mg/L)

The control mortality was 0% at 96 hours.

Test substance : The purity and identification of the test material is not noted. The test material was confirmed by the authors to be AMP-95 (2-Amino-2-methyl-1-propanol).

Reliability : (2) valid with restrictions
2e

19.03.2004 (21)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : = 100 measured/nominal
EC50 : = 193 calculated
Analytical monitoring : yes
Method : other
Year : 1983
GLP : yes
Test substance : Other: AMP

Method : Test procedures per "Methods of Acute Toxicity Tests with Fish, Macroinvertebrates, and Amphibians" (USEPA, 1975) were followed. The daphnia used in the test were cultured at the testing facilities, and the adult daphnia were fed a suspension of trout chow and alfalfa daily until 24 hours prior to testing.

The static Daphnia bioassay was conducted in 250mL beakers containing 200mL of test solution. The vessels were kept at 19-21C, with a 16-hour light / 8 hour dark photocycle.

An initial range-finding study was conducted using 10 Daphnia per concentration level. The range was found by beginning at 0.1 mg/L and increasing the amount of test material by a factor of 10 until a toxic level was found. Once this level had been determined, five concentrations, in duplicate, of the test compound with 10 Daphnia per beaker were selected for their respective bioassay. These concentrations were a logarithmic series ranging from 100 to 1000 mg/L.

Remark : There was no additional data provided on the results of the range-finding study referenced in the methods section.

Result : A computerized program calculated the LC50 for Daphnia based on the method of Stephan et.al. with a 95% CI. The 24-hour LC50 was calculated to be 240 mg/L, and 48-hour LC50 was calculated to be 193 mg/L.

Examination of water quality parameters revealed dissolved oxygen levels ranging from 8.3 mg/L in the control at study start, and levels of 8.5 (control), 8.5 (100mg/L AMP), 8.6 (320 mg/L AMP), and 8.6 mg/L O2 (1000

mg/L AMP) at 48 hours. The pH of the control at study start was 7.8. At 48 hours, the pH data collected was: 8.1 in the control, 8.3 (100mg/L AMP), 8.9 (320 mg/L AMP), and 9.4 (1000 mg/L AMP).

The study was conducted following the intent of the Good Laboratory Practice Regulations.

Test condition : Daphnias (Daphnia magna) first instar < 24 hours old. Test conditions were a temperature range of 19-20C, and a photoperiod of 16 hours light. Test solution (200mL) was placed in 250mL beakers, and ten daphnias were added per test solution. Concentrations tested were in duplicate at 0, 100, 180, 320, 560, and 1000 mg/L AMP-95.

Test substance : AMP-95 (94.31% Active, 5.69% water, NVM 0.0004%.

Lot 216, the same as referenced in the report, "Acute Toxicity Effects of AMP-95 on Bluegill Sunfish, Ninety-Six Hour LC50" (C. Parekh, 1980).

Received as a clear liquid and stored at room temperature.

Reliability : (2) valid with restrictions
2e

19.03.2004 (22)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species : Selenastrum capricornutum (Algae)
Endpoint : growth rate
Exposure period : 4 day(s)
Unit : mg/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 : mg/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-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 : Sub-acute
Species : Rat
Sex : male/female
Strain : Sprague-Dawley
Route of admin. : oral feed
Exposure period : 8 weeks
Frequency of treatm. : Continuous
Post exposure period :
Doses : 0, 1000, 2000, 4000, 8000, 16000 ppm
Control group : yes, concurrent vehicle
LOAEL : ca. 1000 ppm
Method :
Year : 1976
GLP :
Test substance : other TS: P-1826 (assumed to be AMP-regular)
Method : The test material was fed in the diet at dosage levels of 1000, 2000, 4000, 8000, 16000 ppm. Ten male and 10 female rats were used at each dose level and also in a control group. The compound was mixed with distilled water so that the same total volume of liquid was mixed with the food for each group. The compound-water premix was mixed with a small amount of diet, and the food premix was mixed with the total diet. Control rats also received distilled water in their diet at the same volume as the treated diets.

Rats were observed daily for changes in general behavior and appearance. Individual body weights and sex group food consumption were recorded weekly.

At the termination of the study, all surviving rats at the 8000ppm and 16000ppm doses were necropsied. In addition, 2 males and 2 females at each of the other dose levels plus control were likewise necropsied. Livers plus any gross lesions from all animals necropsied were paraffin embedded, sectioned, and stained and examined microscopically.
Remark : Estimated test material intake on week 4, based on mean body weights

and food consumption:

MALES

Dose Group	Material Intake (mg/kg/day)
Control	0
1000ppm	244
2000ppm	474
4000ppm	912
8000ppm	1901
16000ppm	4698

FEMALES

Dose Group	Material Intake (mg/kg/day)
Control	0
1000ppm	436
2000ppm	806
4000ppm	1628
8000ppm	3424
16000ppm	7579

Result : In-life observations made beginning week 3 included emaciation, rough hair coat, and scattered 1x1mm lesions over the dorsal surfaces of a few rats in the 16000ppm group. After week 3, the incidences increased so that all rats in the high dose showed similar clinical signs. Hair loss on the dorsal surface was also noted in rats in this group beginning at week 5 and continuing thereafter. One female rat at the high dose showed general paleness and tremors prior to death at week 2. Two female rats in the 16000ppm group died during the study.

Rats in the 16000ppm group gained slightly less weight as compared to control rats. Gains in the other dose groups were similar to the control. Food consumption patterns were similar for all animals.

At necropsy, all 16000ppm surviving rats, and all rats at the 8000ppm dose level were necropsied. Two males and two females from each of the other groups were also examined. Alopecia and focal skin erosions and ulcerations found in rats at the 16000ppm dose level were viewed as possibly compound related. Hepatocyte vacuolation descrived in rats from all the treated groups, with increasing severity at the higher dose levels, was considered compound related. Microscopic skin lesions found at the 16000ppm dose level, like the corresponding gross lesions, were viewed as possibly compound related.

Test condition : Sixty male (133-183g at study start) and female (115-146g at study start) CD rats were received from Charles River Labs, and were housed individually in hanging canges, maintained in a temperature and humidity controlled room. Purina rodent chow and water were provided to the animals ad libitum.

Conclusion : LOAEL = 1000ppm
LOAEL under these test conditions was 1000ppm. Observed effects at 1000 ppm included alopecia and focal skin erosions.

Reliability : (2) valid with restrictions
2e

(39)

Type : Sub-acute
Species : Mouse
Sex : male/female
Strain : CD-1
Route of admin. : oral feed
Exposure period : 8 weeks
Frequency of treatm. : Continuous
Post exposure period :

Doses : 0, 200, 400, 800, 1600, 3200 ppm
Control group : yes, concurrent vehicle
NOAEL : > 3200 ppm
Method :
Year : 1976
GLP :
Test substance : other TS: P-1826 (assumed to be AMP-regular)
Method : The test material was fed in the diet at dosage levels of 200, 400, 600, 800, 1600, 3200 ppm. Ten male and 10 female mice were used at each dose level and also in a control group. The compound was mixed with distilled water so that the same total volume of liquid was mixed with the food for each group. The compound-water premix was mixed with a small amount of diet, and the food premix was mixed with the total diet. Control mice also received distilled water in their diet at the same volume as the treated diets.

Mice were observed daily for changes in general behavior and appearance. Individual body weights and sex group food consumption were recorded weekly.

At the termination of the study, all surviving mice at the 3200ppm dose were necropsied. In addition, 2 males and 2 females at each of the other dose levels plus control were likewise necropsied. Livers plus any gross lesions from all animals necropsied were paraffin embedded, sectioned, and stained and examined microscopically.

Remark : Estimated test material intake for the animals were calculated based on 4 week body weight and food consumption:

MALES

	Estimated mg/kg/day
Control	0
200ppm	1.244
400ppm	2.088
800ppm	3.360
1600ppm	8.950
3200ppm	14.380

FEMALES

	Estimated mg/kg/day
Control	0
200ppm	1.600
400ppm	3.146
800ppm	6.070
1600ppm	12.870
3200ppm	27.742

Result : No changes considered to be related to compound were seen in the general behavior and appearance. There was no treatment-related mortality. Increases in body weight over the course of the study were comparable for control and all treated animals. Food consumption values were also similar for the control and treated animals.

There were no compound-related gross lesions observed in any of the necropsied mice. There were likewise no microscopic lesions that were considered treatment-related in the livers of any mice necropsied.

Test condition : Sixty male (20-31g at study start) and female (18-27g at study start) CD-1 mice were received from Charles River Labs, and were housed individually in hanging canges, maintained in a temperature and humidity controlled room. Purina rodent chow and water were provided to the animals ad libitum.

Conclusion : The NOAEL for CD-1 mice under these conditions is >3200ppm.

Reliability : (2) valid with restrictions
2e

(40)

Type : Sub-chronic
Species : Rat
Sex : male/female
Strain : other: CD
Route of admin. : Gavage
Exposure period : 13 weeks
Frequency of treatm. : 5 days / week
Post exposure period :
Doses : 0, 500, 750, 1100, 1700 mg/kg at pH of 7 & 11+
Control group : yes, concurrent vehicle
Method :
Year : 1977
GLP :
Test substance : other TS: P-1826 (assumed to be AMP-Regular)

Method : Dose Preparation
The dose solution for pH=11+ was prepared by adding the neat test material to distilled water in order to achieve a concentration adequate to dose the animals 1-5mL of dose solution according to the animals' body weights and dose group. The dose solution of pH=7 was prepared by adding the neat test material to distilled water, neutralizing the solution to pH=7. Because the resulting stock solution is purple in color, the solution was decolored using activated charcoal. The stock solution was then diluted as appropriate to obtain solutions adequate to dose the animals with 1-5mL solution according to their body weights and the targeted dose.

Dose Administration
The solutions were administered 5 days per week for 13 weeks, once per day by oral gavage. The dose was adjusted to the body weight of the rat by administration of different volumes of solution (1-5mL).

In-life Observations & Measures
Animals were observed 5 days/week for pharmacological effects of the test material. The observations were general, including signs of altered food and water consumption, irritability, sedation, hair and cutaneous alterations, external inflammation, hyperventilation, convulsions, neuromuscular paralysis, and altered activity. Body weights were recorded weekly, and dead animals were recorded and autopsied as soon as discovered.

Hematology & Clinical Chemistry Measures
The following blood parameters were measured: hemaglobin, packed cell colume (hematocrit), erythrocyte count, leucocyte count, differential count, transaminases, glutamic-oxalacetic and glutamic-pyruvic, total protein, blood urea nitrogen (BUN), Sodium, Potassium, Chloride, and Creatinine. For urine, Ph, protein, occult blood, glucose, bilirubin, sediment, and specific gravity were measured.

Pathology
Only gross pathology was reported.

Result : Mortality
A high mortality rate was recorded for animals with the pH=11 doses. No treatment-related mortality was noted for the pH=7 groups.

Behavior and Appearance
General observations on the pH=11 groups included hyperventilation and respiratory difficulty, neither of which could be confirmed at necropsy. Non-treatment related pneumonia was noted in some rats. Rats generally showed hyperirritability and hyperactivity at the time of AMP administration.

In the pH=11 rats receiving more than 750mg/kg, abdominal swelling, nasal and mouth bleeding were noted the first few days of the study. The abdominal swelling was always followed by death. Some loss of hair around the mouth and face was noted for pH=11 rats, and assumed to be treatment-related. General observations for rats receiving the dose at pH=7 were hyperventilation (lesser extent than pH=11 rats), and limited hyperactivity and hyperirritability. Some of the rats also showed loss of hair around the mouth and face. In a few rats, the effect was accompanied by skin ulceration due likely to excessive salivation, or a local irritancy by the compound.

Body Weight, Food Consumption Trends
There was no significant difference in the rate of body weight change between all dose groups relative to the controls. Food and water consumption were qualitatively noted. Food consumption appeared normal, while AMP-administered rats appeared to drink more frequently than controls.

Hematology & Clinical Chemistry
Neither the pH=7 or pH=11 females showed significant differences in hematocrit, hemoglobin, erythorcyte counts, or leukocytes. The males from the pH=11 group in the 1100 mg/kg dose group showed a significant decrease in hematocrit, hemoglobin, and red blood cell count due to a loss of blood.

pH 11 group males

Group	HCT	HgB	RBC(x10^6)	WBC
Control (10)	44+-1	16.5+-0.4	7.41+-0.29	8.2+-1.2
500mg/kg (8)	43+-1	16.7+-0.9	6.20+-0.47	13.6+-2.6
750mg/kg (7)	43+-1	16.2+-0.5	6.31+-0.34	9.4+-2.5
1100mg/kg(2)	40+-1	14.9+-0.3	5.94+-0.10	9.0+-1.6
1700mg/kg	(none surviving)			

A slight but significant decrease is seen in the RBC of rats receiving 500 and 750 mg/kg AMP. There was no significant effect on hematocrit at these exposure levels. The pH=7 group (only at 1700mg/kg) showed significant decreases in hematocrit and hemoglobin.

pH 7 group

Group	HCT	HgB
Control (10)	46+-1	17.1+-0.1
500mg/kg (9)	43+-2	16.4+-0.5
750mg/kg (10)	42+-1	16.4+-0.6
1100mg/kg(10)	42+-1	16.4+-0.8
1700mg/kg (9)	40+-1	15.1+-0.2

No significant differences were measured in Na, K, Cl, Ca, total serum protein, BUN, or creatinine for either pH group at any dose level. SGPT values were within normal ranges for all dose groups except for pH=7 females at 1700mg/kg, and pH=7 males at 1000 and 1700 mg/kg, where the values were significantly elevated.

Urinalysis
Urinalysis was performed only for the pH=11 groups. The data indicated some proteinuria.

Gross Pathology
There were no treatment-related grossly-recognizable changes observed at necropsy.

Test condition : CD rats were received from Charles River weighing 90-100g, and were acclimated a minimum of one week to the laboratory prior to the experimental start. The rats were divided into groups of 10 per sex per

dose level, for each of 2 pH's. They were housed in groups of 2-3 per plastic cage, and fed via overhead racks. Food and water was provided ad libitum and animals were housed in rooms with controlled temperature, humidity, and photocycles.

Conclusion : LOAEL and NOAEL cannot be established because the authors do not specifically state, or provide detailed data regarding the lowest dose level at which in-life observations (respiratory difficulty, hyperirritability, hyperactivity, etc.) were seen.

Reliability : (2) valid with restrictions
2e (41)

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 (42)

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 (43)

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 (43)

Type	:	other: Mechanism of nucleolysis in DNA
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 (44)

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 (43)

Type : Bacterial reverse mutation assay
System of testing : S. typhimurium (tester strains TA98, TA100, TA1535, TA1537) and E.coli (tester strain WP2 uvrA)
Test concentration : 100-5000 ug per plate
Cycotoxic concentr. :
Metabolic activation : with and without
Result : Negative
Method : OECD Guide-line 471
Year : 1996
GLP : Yes
Test substance : Other TS:AMP
Method : Positive controls, appropriate to the given tester strains, were used, and the concentration varied according to positive control compound. The sterility of the test article was verified.

Preliminary Toxicity Assay
Ten dose levels of the test article were plated, one plate per dose, with overnight cultures of TA100 and WP2 uvrA on selective minimal agar in the presence and absence of rat liver S9 activation.

Mutagenicity Assay
An initial and confirmatory assay was used to evaluate the mutagenic potential of the test material. A minimum of 5 dose levels of the test article,

with vehicle and positive controls, were plated with tester strains in the presence and absence of rat liver S9 activation. All dose levels of test article, vehicle controls, and positive controls were plated in triplicate. The test systems were exposed to the test article via the plate incorporation methodology described by Ames, et.al.((1975) and updated by Maron and Ames (1983). Plates were coded according to the testing laboratory's standard procedures. Plates were incubated for 48-72 hours at 35-39C. Plates not counted immediately following the incubation period were stored at 2-6C until the colonies could be counted.

Toxicity and degree of precipation were scored relative to the vehicle control plate using a well-defined 9-point scale. Colonies were counted either by an automated colony counter or by hand unless the assay was preliminary or the plate exhibited toxicity. Plates exhibiting test article precipitate that interferes with an automated colony counter were counted by hand.

Mean and standard deviation of the number of revertants per plate were calculated and reported. For a positive finding, the test material must cause a dose-related increase in mean revertants per plate of at least one tester strain with a minimum of 2 increasing concentrations of test article. Positive finding for TA1535 and TA1537 is an increase in mean revertants at the peak of dose-response greater than, or equal to, 3x mean control value. Positive finding for TA98, TA100, WP2 uvrA is an increase in mean revertants at the peak of dose-response greater than, or equal to, 2x mean control value.

Remark : GLP's were followed except for the following exceptions:
1. The identity, strength, purity, and composition or other characteristics to define the test or control article were not determined by the testing facility.
2. Analyses to determine the uniformity, concentration, or stability of the test or control mixtures were not performed by the testing facility.
3. The stability of the test or control article under the test conditions was not determined by the testing facility.

Result : Water was selected as the solvent of choice. The test material was soluble in water at approximately 100ug.mL, the maximum concentration tested.

Preliminary Toxicity Assay
The maximum dose tested was 5000ug/plate, achieved by using a concentration of 100mg/mL and a 50uL plating aliquot. Based on the findings, the maximum dose plated in the mutagenicity assay was 5000ug/plate. Neither precipitate nor appreciable toxicity was observed.

Mutagenicity Assay
Neither precipitate nor appreciable toxicity was observed in the initial or confirmatory assays. In neither the initial nor confirmatory assay was there a positive response with any of the tester strains at any dose level, in the presence or absence of S9 activation.

Test condition : Salmonella tester strains were recieved directly from Dr. Bruce Ames, University of California, Berkeley, and the E.coli was received from the National Collection of Industrial and Marine Bacteria, Aberdeen, Scotland.

Tester strains TA98 and TA1537 are reverted from histidine dependence (auxotrophy) to histidine independence (prototrophy) by frameshift mutagens. Tester TA1535 is reverted by mutagens that cause basepair substitutions. Tester TA100 is reverted by mutagens that cause both frameshift and basepair substitution mutations. Specificity of the reversion mechanism in E.coli is sensitive to basepair substitution mutations, rather than frameshift mutations.

To assure that cultures were harvested in late log phase, the length of incubation was controlled and monitored. Each culture wasmonitored spectrophotometrically for turbidity and was harvested at a percent

transmittance yielding a titer of approximately 10^9 cells per milliliter.

Acoclor 1254-induced rat liver S9 was used for the metabolic activation system. The S9 was prepared from male Sprague-Dawley rats induced with a single IP injection of Acroclor 1254, 500mg/kg, five days prior to sacrifice. Each batch was assayed for its ability to metabolize.

Conclusion : The results of this study indicate that, under the conditions of this study, the test material did not cause a positive response with any of the tester strains in the presence and absence of Acrclor-induced rat liver S9.

Reliability : (1) valid without restriction
1a

(45)

Type : Mammalian cell gene mutation assay
System of testing : L5178Y/TK+- Mouse Lymphoma
Test concentration : 5000 ug/mL
Cycotoxic concentr. :
Metabolic activation : with and without
Result : Negative
Method : OECD Guide-line 476
Year : 1996
GLP : Yes
Test substance : other TS: AMP-95
Method : Aroclor 1254-induced rat liver S9 was used as the metabolic activation system.

A preliminary toxicity assay was used to establish the optimal dose levels for the mutagenesis assay. L5178Y cells were exposed to the vehicle alone and to concentrations of the test article ranging from 0.5-5000 uL in both the absence and presence of S9-activation. Cell population density was determined at 24 and 48 hours after exposure to the test article. Toxicity was measured as suspension of growth relative to the growth of the solvent controls. The mutagenesis assay, initial and independent repeat, was used to evaluate the mutagenic potential of the test article. L5178Y mouse lymphoma cells were exposed to the vehicle alone and 10 concentrations of the test article in both the absence and presence of S9. Positive controls, with and without S9, were tested concurrently.

Tubes containing L5178Y/TK+- cells with F0P medium or S9 activation mixture, and 100uL of test solution at 10 concentrations were prepared. Positive controls treated with MMS and 7,12-DMBA were also prepared. Treatment tubes were gassed with CO2 and incubated in the dark for 4 hours. Cells were washed twice, resuspended, gassed with CO2 in air again, and placed on a roller. Cells were counted, and numbers were adjusted if necessary. For expression of TK+- cells, cells were placed in a cloning meduim of granulated agar, mixed with Trifluorothymidine (TFT) or viable count, prewarmed and filled with cloning media. The tubes were centrifuged, supernatant decanted, and cells resuspended in cloning media. . Tests were done in duplicate. TFT or Viable Count were added to the floask and placed on a shaker. The suspension was placed in petri dishes, placed in cold storage for 30 minutes, then incubated for 10-14 days.

Diameters and numbers of colonies were recorded, and analyzed relative to positive and solvent controls. Previous published data indicates that the large colony mutants received localized damage, likely in the form of a point mutation or small deletion within the TK locus, and small colony mutants received damage to collateral loci concordant with the loss of TK activity.

Remark : Study followed GLP's except for the following:
1. The identity, strength, purity, and composition or other characteristics to define the test or control article were not determined by the testing facility.

2. Analyses to determine the uniformity, concentration, or stability of the test or control mixtures were not performed by the testing facility.
3. The stability of the test or control article under the test conditions was not determined by the testing facility.

Result : Sterile distilled water was the solvent of choice. The test material was miscible in water at 500 mg/mL, the maximum tested concentration.

Preliminary Toxicity Assay
The high dose tested was 5000ug/mL. Osmolality of the solvent control was 300mmol/kg and of the highest dose was 396mmol/kg. Suspension growth relative to the solvent control was 13% at 5000ug/mL without S9 activation, and 31% with S9 activation. Based on these results, the dose levels chosen for the mutagenesis assay ranged from 500-5000ug/mL for both the non-activated and S9-activated cultures.

Mutagenesis Assay
In the non-activated system, cultures treated with 1000-500ug/mL were cloned and produced a range in suspension growth of 11-55%. In the S9-activated system, cultures treated with 500-5000ug/mL were cloned and produced a range in suspension growth of 9-98%.
No treated cultures exhibited mutant frequencies more than 55 mutants per 10^6 clonable cells over the solvent control. A dose-response trend was not observed in either the activated or non-activated systems. Over the concentration ranges, total growth for the non-activated cultures ranged from 12-60%, and 10-137% for the S9-activated cultures. Results of the independent repeat assay are similar (12-62% and 32-124% for non-activated and S9-activated system suspension growth, respectively; 14-67% and 29-191% for non-activated and S9-activated system total growths, respectively). There was likewise no increase in mutant frequencies over the solvent control. Colony sizing for the positive control yielded the expected increase in small colonies, thereby verifying the methods used to detect small colony mutants.

Conclusion : The results of the L5178Y/TK+- Mouse Lymphoma Mutagenesis Assay indicate that, under the conditions of this study, 2-amino-2-methyl-1-propanol did not cause a positive response in the non-activated and S9-activated systems, and was concluded to be negative.

Reliability : (1) valid without restriction
1a

(46)

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 (43)

Type : Micronucleus assay
Species : Mouse
Sex :
Strain : ICR
Route of admin. : i.p.
Exposure period : 1 ip injection
Doses : vehicle control, 16, 30, 60 mg/kg, and positive control CP (50mg/kg)
Result : Negative
Method : OECD Guide-line 474 "Genetic Toxicology: Micronucleus Test"
Year : 1998
GLP : Yes
Test substance : other TS: AMP-95 (lot 35662)
Method : In each the Pilot & Toxicity Studies (designed to set appropriate dose levels for the micronucleus assay), and the Micronucleus Assay, mice were weighed immediately prior to dose administration and the dose volume was based on individual body weights. They were observed after dosing, and daily thereafter for 3 days for clinical signs of chemical effects. Body weights were recorded prior to dose administration and 1 and 3 days after dosing. Mice were given a single IP injection of the test article in water, the vehicle alone, or the positive control substance.

Pilot Study: 2 male mice were dosed with 1, 10, 100, or 1000 mg test material /kg body weight, and 5 males and 5 females were dosed with 2000 mg/kg.

Toxicity Study:
5 male and 5 female mice were dosed with 200, 400, 600, 800 mg/kg.

Based on the results of the pilot and toxicity studies, the high dose for the micronucleus test was set at 60 mg/kg, which was estimated to be approximately 80% of the LD50/3.

Micronucleus Assay:
Male and female mice were dosed with 16, 30, or 60 mg/kg via a single IP injection of the test material. At the scheduled sacrifice times, up to 5 mice / sex / dose were sacrificed, the femurs exposed, and bone marrow aspirated into a syringe of fetal bovine serum. The bone marrow cells were pelleted by centrifugation and the supernatant drawn off. The cells were resuspended and a small amount of suspension spread onto a glass slide. Two to four slides were prepared per animal. The slides were fixed in methanol, stained, and permanently mounted. Slides were coded and scored blindly. Using oil immersion, 2000 polychromatic erythrocytes were scored for the presence of micronuclei. The number of micronucleated normochromatic erythrocytes in the field of 2000 polychromatic erythrocytes was enumerated. The proportion of polychromatic erythrocytes to total erythrocytes was also recorded per 1000 erythrocytes. Statistical significance was determined using the Kastenbaum-Bowman tables which are based on the binomial distribution.

The test article was considered to induce a positive response if a dose-responsive increase in mocronucleated polychromatic erythrocytes was observed and one or more doses were statistically-elevated relative to the

vehicle control (p>0.05) at any sampling time. If a single dose group was significantly elevated without a dose-response trend, the assay was considered a suspect or unconfirmed positive and a repeat assay recommended. The test article would be considered negative if no statistically significant increase in micronucleated polychromatic erythrocytes above the concurrent vehicle control was observed at any sampling time.

Remark : Exceptions to GLP's included:
1. The identity, strength, purity, and composition or other characteristics to define the test or control article were not determined by the testing facility.
2. Analyses to determine the uniformity, concentration, or stability of the test or control mixtures were not performed by the testing facility.
3. The stability of the test or control article under the test conditions was not determined by the testing facility.

Result : Pilot:
Mortality occurred within 4 hours following dosing: 5/5 males and 5/5 females at 2000 mg/kg, and 2/2 males at 1000 mg/kg. There were no clinical observations noted.

Toxicity:
Mortality occurred within 3 days of dosing: 5/5 males and 5/5 females at 400, 600, and 800 mg/kg, and 3/5 males and 5/5 females at 200 mg/kg. Clinical signs included: lethargy in males and females at all dose levels, piloerection in males and females, and crusty eyes in males at 200 mg/kg. The LD50/3 was calculated by probit analysis to be approximately 73.7 mg/kg for male and female mice.

Micronucleus Assay:
There was no treatment-related mortality at any dose level. Clinical signs noted on the day of dosing included: lethargy in males and females at 60 mg/kg (highest dose). All other mice treated with test material and control articles appeared normal during the study. The number of micronucleated polychromatic erythrocytes per 2000 polychromatic erythrocytes in test article-treated groups was not statistically increased relative to their respective vehicle control in either male of female mice, regardless of dose level or bone marrow collection time.

Test condition : ICR mice from Harlan Sprague-Dawley, INC, were 6-8 weeks old at study initiation. For the pilot, toxicity, and MNT assay, males ranged in weight from 27.4g to 31.9g, and females ranged from 23.0g to 28.0g. After arrival to the lab, the animals were monitored for parasites and infections, and were quarantined a minimum of 5 days. They were observed daily for general health, food and water consumption patterns, and other conditions. The animals were deemed healthy prior to placement on study.

Mice were housed in an AALAC-accredited facility with appropriate temperature, humidity, and photocycle for the species. They were housed up to 5 per cage, and given food and water ad libitum. The feed and water contained no contaminants that influenced the study.

The mice were randomized and placed into assigned dose groups, and were identified by a uniquely numbered ear tag.

Conclusion : Under the conditions of the assay described in this report, 2-amino-2-methyl-1-propanol did not induce a sugnificant increase in the incidence of micronucleated polychromatic erythrocytes in bone marrow, and was concluded to be negative in the micronucleus test using male and female ICR mice.

Reliability : (1) valid without restriction
1a

(47)

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 (42)

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 (48)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

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 (49)

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 (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 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 (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.
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 (52)

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 (53)

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 (54)

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 (55)

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 (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 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 (57)

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 (58)

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 (59)

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 (60)

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 (61)

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 (62)

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 (63)

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 (64)

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 (65)

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 (66)

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